(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

PCT

(10) International Publication Number
WO 02/060900 A2

(51) International Patent Classification[7]: C07D 471/00

(21) International Application Number: PCT/US02/03016

(22) International Filing Date: 30 January 2002 (30.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/265,841 31 January 2001 (31.01.2001) US

(71) Applicants: **TELIK, INC.** [US/US]; 750 Gateway Boulevard, South San Francisco, CA 94080 (US). **SANWA KAGUKU KENKYUSHO CO., LTD.** [—/—]; 35 Higashisotobori-cho, Higashi-Ku, Nagoya 461-8631 (JP).

(72) Inventors: **LABORDE, Edgardo**; 799 Pitcairn Drive, Foster City, CA 94404 (US). **ROBINSON, Louise**; 1349 Rosewood Avenue, San Carlos, CA 94070 (US). **MENG, Fanying**; 783 Sweeny Street, San Francisco, CA 94134 (US). **PETERSON, Brian, T.**; 80 Dawnview Way, San Francisco, CA 94131 (US). **VILLAR, Hugo, O.**; 5549 Soledad Mountain Road, La Jolla, CA 92037 (US). **ANUSKIEWICZ, Steven, E.**; 335 Palomar Court, San Bruno, CA 94066 (US). **ISHIWATA, Yoshiro**; 1-2 Nagakute Aza-arata, Nagakute-cho, Aichi-gun, Aichi Prefecture 408-1131 (JP). **YOKOCHI, Shoji**; 1-31-6 Sasaonishi, Toin-cho, Inabe-gun, Mie Prefecture 511-0231 (JP). **MATSUMOTO, Yukiharu**; 2-61-2 Kako-machi, Gifu-shi, Gifu Prefecture 500-8259 (JP). **KAKIGAMI, Takuji**; 2735-1 Ageki, Hokusei-cho, Inabe-gun, Mie Prefecture 511-0428 (JP). **INAGAKI, Hideaki**; 1-4-19 Imahon-machi, Anjoh-shi, Aichi Prefecture 446-0008 (JP). **JOMORI, Takahito**; 3-22 Ohari, Meito-ku, Nagoya-shi 465-0064 (JP). **MATSUSHIMA, Kouji**; 159-1 Matsudo, Matsudo-shi, Chiba Prefecture 271-0092 (JP).

(74) Agent: **HEUSCH, Marina, I.**; Heller Ehrman White & McAuliffe LLP, 275 Middlefield Road, Menlo Park, CA 94025-3506 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), DE (utility model), DK (utility model), DM, DZ, EC, EE (utility model), ES, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/060900 A2

(54) Title: ANTAGONISTS OF MCP-1 FUNCTION AND METHODS OF USE THEREOF

(57) Abstract: The present invention relates to chemical compounds, pharmaceutical compositions comprising said compounds, uses of said compounds and compositions, methods of treatment employing said compounds and compositions, and processes for preparing said compounds. Specifically, this invention relates to novel compounds which are antagonists of MCP-1 function and are useful in the prevention or treatment of chronic or acute inflammatory or autoimmune diseases, especially those associated with aberrant lymphocyte or monocyte accumulation such as arthritis, asthma, atherosclerosis, diabetic nephropathy, inflammatory bowel disease, Crohn's disease, multiple sclerosis, nephritis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, and transplant rejection. More specifically, the invention is related to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases.

ANTAGONISTS OF MCP-1 FUNCTION AND METHODS OF USE THEREOF

FIELD OF THE INVENTION

The present invention relates to chemical compounds, pharmaceutical compositions comprising said compounds, uses of said compounds and compositions, methods of treatment employing said compounds and compositions, and processes for preparing said compounds. Specifically, this invention relates to novel compounds which are antagonists of MCP-1 function and are useful in the prevention or treatment of chronic or acute inflammatory or autoimmune diseases, especially those associated with aberrant lymphocyte or monocyte accumulation such as arthritis, asthma, atherosclerosis, diabetic nephropathy, inflammatory bowel disease, Crohn's disease, multiple sclerosis, nephritis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, and transplant rejection. More specifically, the invention is related to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases.

BACKGROUND OF THE INVENTION

Chemokines: Structure and Function

The migration of leukocytes from blood vessels into diseased tissues is an important process in the initiation of normal inflammatory responses to certain stimuli or insults to the immune system. However, this process is also involved in the onset and progression of life-threatening inflammatory and autoimmune diseases; blocking leukocyte recruitment in these disease states, therefore, can be an effective therapeutic strategy.

The mechanism by which leukocytes leave the bloodstream and accumulate at inflammatory sites involves three distinct steps: (1) rolling, (2) arrest and firm adhesion, and (3) transendothelial migration [Springer, *Nature* 346:425-433 (1990); Lawrence and Springer, *Cell* 65:859-873 (1991); Butcher,

Cell 67:1033-1036 (1991)]. The second step is mediated at the molecular level by chemoattractant receptors on the surface of leukocytes which bind chemoattractant cytokines secreted by proinflammatory cells at the site of damage or infection. Receptor binding activates leukocytes, increases their adhesiveness to the endothelium, and promotes their transmigration into the affected tissue, where they can secrete inflammatory and chemoattractant cytokines and degradative proteases that act on the subendothelial matrix, facilitating the migration of additional leukocytes to the site of injury.

The chemoattractant cytokines, collectively known as "chemokines," are a large family of low molecular weight (8 to 10 kD) proteins that share the ability to stimulate directed cell migration ("chemotaxis") [Schall, *Cytokine* 3:165-183 (1991); Murphy, *Rev Immun* 12:593-633 (1994)].

Chemokines are characterized by the presence of four conserved cysteine residues and are grouped into two main subfamilies based on whether the two amino-terminal cysteines are separated by one amino acid (CXC subfamily, also known as α-chemokines) or immediately adjacent to each other (CC subfamily, also referred to as β-chemokines) [Baggiolini et al., *Adv Immunol* 55:97-179 (1994); Baggiolini et al., *Annu Rev Immunol* 15:675-705 (1997); Deng et al., *Nature* 381:661-666 (1996); Luster, *New Engl J Med* 338:436445 (1998); Saunders and Tarby, *Drug Discovery Today* 4:80-92 (1999)].

The chemokines of the CXC subfamily, represented by IL-8, are produced by a wide range of cells and act predominantly on neutrophils as mediators of acute inflammation. The CC chemokines, which include MCP-1, RANTES, MIP-1α, and MIP-1β, are also produced by a variety of cells, but these molecules act mainly on monocytes and lymphocytes in chronic inflammation.

Like many cytokines and growth factors, chemokines utilize both high and low affinity interactions to elicit full biological activity. Studies performed with labeled ligands have identified chemokine binding sites ("receptors") on the surface of neutrophils, monocytes, T cells, and eosinophils with affinities in the 500 pM to 10 nM range [Kelvin et al., *J Leukoc Biol* 54:604-612 (1993); Murphy, *Annu Rev Immunol* 12:593-633 (1994); Raport et al., *J Leukoc Biol* 59:18-23 (1996); Premack and Schall, *Nature* Med 2:1174-1178 (1996)]. The cloning of

these receptors has revealed that cell surface high-affinity chemokine receptors belong to the seven transmembrane ("serpentine") G-protein-coupled receptor (GPCR) superfamily.

Chemokine receptors are expressed on different cell types, including non-leukocyte cells. Some receptors are restricted to certain cells (*e.g.*, the CXCR1 receptor is predominantly restricted to neutrophils), whereas others are more widely expressed (*e.g.*, the CCR2 receptor is expressed on monocytes, T cells, natural killer cells, dendritic cells, and basophils).

Given that at least twice as many chemokines have been reported to date as there are receptors, there is a high degree of redundancy in the ligands and, not surprisingly, most chemokine receptors are rather promiscuous with regard to their binding partners. For example, both MIP-1α and RANTES bind to the CCR1 and CCR4 receptors, while MCP-1 binds to the CCR2 and CCR4 receptors. Although most chemokines receptors bind more than one chemokine, CC receptors bind only CC chemokines, and CXC receptors bind only CXC chemokines. This ligand-receptor restriction may be related to the structural differences between CC and CXC chemokines, which have similar primary, secondary, and tertiary structures, but different quaternary structures [Lodi et al., *Science* 263:1762-1767 (1994)].

The binding of chemokines to their serpentine receptors is transduced into a variety of biochemical and physiological changes, including inhibition of cAMP synthesis, stimulation of cytosolic calcium influx, upregulation or activation of adhesion proteins, receptor desensitization and internalization, and cytoskeletal rearrangements leading to chemotaxis [Vaddi et al., *J Immunol* 153:4721-4732 (1994); Szabo et al., *Eur J Immunol* 27:1061-1068 (1997); Campbell et al., *Science* 279:381-384 (1998); Aragay et al., *Proc Natl Acad Sci USA* 95:2985-2990 (1998); Franci et al., *J Immunol* 157:5606-5612 (1996); Aramori et al., *EMBO J* 16:4606-4616 (1997); Haribabu et al., *J Biol Chem* 272:28726-28731 (1997); Newton et al., *Methods Enzymol* 287:174-186 (1997)]. In the case of macrophages and neutrophils, chemokine binding also triggers cellular activation, resulting in lysozomal enzyme release and generation of toxic products from the respiratory burst [Newton et al., *Methods Enzymol* 287:174-

186 (1997); Zachariae et al., *J Exp Med* 171:2177-2182 (1990); Vaddi et al., *J Leukocyte Biol* 55:756-762 (1994)]. The molecular details of the chemokine-receptor interactions responsible for inducing signal transduction, as well as the specific pathways that link binding to the above-mentioned physiological changes, are still being elucidated. Notwithstanding the complexity of these events, it has been shown that in the case of the MCP-1/CCR2 interaction, specific molecular features of MCP-1 can induce different conformations in CCR2 that are coupled to separate post-receptor pathways [Jarnagin et al., *Biochemistry* 38:16167-16177 (1999)]. Thus, it should be possible to identify ligands that inhibit chemotaxis without affecting other signaling events.

In addition to their high-affinity seven transmembrane GPCRs, chemokines of both subfamilies bind to various extracellular matrix proteins such as the glycosaminoglycans (GAGs) heparin, chondroitin sulfate, heparan sulfate, and dermatan sulfate with affinities in the middle nanomolar to millimolar range. These low-affinity chemokine-GAG interactions are believed to be critical not only for conformational activation of the ligands and presentation to their high-affinity serpentine receptors, but also for the induction of stable chemokine gradients that may function to stimulate haptotaxis (*i.e.*, the migration of specific cell subtypes in response to a ligand gradient that is affixed upon the surface of endothelial cells or embedded within the extracellular matrix) [Witt and Lander, *Curr Biol* 4:394-400 (1994); Rot, *Eur J Immunol* 23:303-306 (1993); Webb et al., *Proc Natl Acad Sci USA* 90:7158-7162 (1993); Tanaka et al, *Nature* 361:79-82 (1993); Gilat et al., *J Immunol* 153:4899-4906 (1994)]. Similar ligand-GAG interactions have been described for a variety of cytokines and growth factors, including the various members of the FGF family, hepatocyte growth factor, IL-3 and IL-7, GM-CSF, and VEGF [Roberts et al., *Nature* 332:376-378 (1988); Gilat et al., *Immunol Today* 17:16-20 (1996); Clarke et al., *Cytokine* 7:325-330 (1995); Miao et al., *J Biol Chem* 271:4879-4886 (1996); Vlodavsky et al., *Cancer Metastasis Rev* 15:177-186 (1996)].

MCP-1 and Diseases

Chemokines have been implicated as important mediators of allergic, inflammatory and autoimmune disorders and diseases, such as asthma, atherosclerosis, glomerulonephritis, pancreatitis, restenosis, rheumatoid arthritis, diabetic nephropathy, pulmonary fibrosis, and transplant rejection. Accordingly, it has been postulated that the use of antagonists of chemokine function may help reverse or halt the progression of these disorders and diseases.

In particular, elevated expression of MCP-1 has been observed in a number of chronic inflammatory diseases [Proost et al., *Int J Clin Lab Res* 26:211-223 (1996); Taub, D. D. *Cytokine Growth Factor Rev* 7:355-376 (1996)] including rheumatoid arthritis [Robinson et al., *Clin Exp Immunol* 101:398-407 (1995); Hosaka et al., *ibid.* 97:451-457 (1994); Koch et al., *J Clin Invest* 90:772-779 (1992); Villiger et al., *J Immunol* 149:722-727 (1992)], asthma [Hsieh et al., *J Allergy Clin Immunol* 98:580-587 (1996); Alam et al., *Am J Respir Crit Care Med* 153:1398-1404 (1996); Kurashima et al., *J Leukocyte Biol* 59:313-316 (1996); Sugiyama et al., *Eur Respir J* 8:1084-1090 (1995)], and atherosclerosis [Yla-Herttuala et al., *Proc Natl Acad Sci USA* 88:5252-5256 (1991); Nelken et al., *J Clin Invest* 88:1121-1127 (1991)].

MCP-1 appears to play a significant role during the early stages of allergic responses because of its ability to induce mast cell activation and LTC4 release into the airway, which directly induces AHR (airways hyper-responsiveness) [Campbell et al., *J Immunol* 163:2160-2167 (1999)].

MCP-1 has been found in the lungs of patients with idiopathic pulmonary fibrosis and is thought to be responsible for the influx of mononuclear phagocytes and the production of growth factors that stimulate mesenchymal cells and subsequent fibrosis [Antoniades et al., *Proc Natl Acad Sci USA* 89:5371-5375 (1992)]. In addition, MCP-1 is also involved in the accumulation of monocytes in pleural effusions which is associated with both *Mycobacterium tuberculosis* infection and malignancy [Strieter et al., *J Lab Clin Med* 123:183-197 (1994)].

MCP-1 has also been shown to be constitutively expressed by synovial fibroblasts from rheumatoid arthritis patients, and its levels are higher in

rheumatoid arthritis joints compared to normal joints or those from other arthritic diseases [Koch et al., *J Clin Invest* 90:772-779 (1992)]. These elevated levels of MCP-1 are probably responsible for the monocyte infiltration into the synovial tissue. Increased levels of synovial MIP-1α and RANTES have also been detected in patients with rheumatoid arthritis [Kundel et al., *J Leukocyte Biol* 59:6-12 (1996)].

MCP-1 also plays a critical role in the initiation and development of atherosclerotic lesions. MCP-1 is responsible for the recruitment of monocytes into atherosclerotic areas, as shown by immunohistochemistry of macrophage-rich arterial wall [Yla-Herttuala et al., *Proc Natl Acad Sci USA* 88:5252-5256 (1991); Nelken et al., *J Clin Invest* 88:1121-1127 (1991)] and anti-MCP-1 antibody detection [Takeya et al., *Human Pathol* 24:534-539 (1993)]. LDL-receptor/MCP-1-deficient and apoB-transgenic/MCP-1-deficient mice show significantly less lipid deposition and macrophage accumulation throughout their aortas compared with wild-type MCP-1 strains [Alcami et al., *J Immunol* 160:624-633 (1998); Gosling et al., *J Clin Invest* 103:773-778 (1999); Gu et al., *Mol. Cell.* 2:275-281 (1998); Boring et al., *Nature* 394:894-897 (1998).

Other inflammatory diseases marked by specific site elevations of MCP-1 include multiple sclerosis (MS), glomerulonephritis, and stroke.

These findings suggest that the discovery of compounds that block MCP-1 activity would be beneficial in treating inflammatory diseases.

Antagonists of Chemokine Function

Most chemokine antagonists reported to date are either neutralizing antibodies to specific chemokines or receptor-ligand antagonists, that is, agents that compete with specific chemokines for binding to their cognate serpentine receptors but, unlike the chemokines themselves, do not activate these receptors towards eliciting a functional response [Howard et al., *Trend Biotechnol* 14:46-51 (1996)].

The use of specific anti-chemokine antibodies has been shown to curtail inflammation in a number of animal models (*e.g.*, anti-MIP-1α in bleomycin-induced pulmonary fibrosis [Smith et al., *Leukocyte Biol* 57:782-787 (1994)];

anti-IL-8 in reperfusion injury [Sekido et al., *Nature* 365:654-657 (1995)], and anti-MCP-1 in a rat model of glomerulonephritis [Wada et al., *FASEB J* 10:1418-1425 (1996)]). In the MRL-*lpr* mouse arthritis model, administration of an MCP-1 antagonist significantly reduced the overall histopathological score after the early onset of the disease [Gong et al., *J Exp Med* 186:131-137 (1997)].

A major problem associated with using antibodies to antagonize chemokine function is that they must be humanized before use in chronic human diseases. Furthermore, the ability of multiple chemokines to bind and activate a single receptor forces the development of a multiple antibody strategy or the use of cross-reactive antibodies in order to completely block or prevent pathological conditions.

Several small molecule antagonists of chemokine receptor function have been reported in the scientific and patent literature [White, *J. Biol Chem* 273:10095-10098 (1998); Hesselgesser, *J. Biol Chem* 273:15687-15692 (1998); Bright et al., *Bioorg Med Chem* Lett 8:771-774 (1998); Lapierre, *26th Natl Med Chem Symposium*, June 14-18, Richmond (VA), USA (1998); Forbes et al., *Bioorg Med Chem* Lett 10:1803-18064 (2000); Kato et al., WO Patent 97/24325; Shiota et al., WO Patent 97/44329; Naya et al., WO Patent 98/04554; Takeda Industries, JP Patent 0955572 (1998); Schwender et al., WO Patent 98/02151; Hagmann et al., WO Patent 98/27815; Connor et al., WO Patent 98/06703; Wellington et al., US Patent 6,288,103 B1 (2001)].

The specificity of the chemokine receptor antagonists, however, suggests that inflammatory disorders characterized by multiple or redundant chemokine expression profiles will be relatively more refractory to treatment by these agents.

A different approach to target chemokine function would involve the use of compounds that disrupt the chemokine-GAG interaction. One class of such agents with potential therapeutic application would consist of small organic molecules that bind to the chemokine low affinity GAG-binding domain.

Compounds of this class might not inhibit binding of the chemokine to its high-affinity receptor *per se*, but would disrupt chemokine localization within the extracellular matrix and provide an effective block for directed leukocyte-taxis

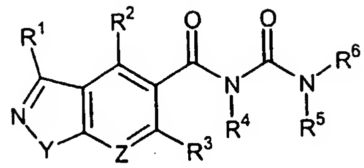
within tissues. An advantage of this strategy is the fact that most CC and CXC chemokines possess similar C-terminal protein folding domains that define the GAG-binding site, and, hence, such compounds would be more useful for the treatment of inflammatory disorders induced by multiple, functionally redundant chemokines [McFadden and Kelvin, *Biochem Pharmacol* 54:1271-1280 (1997)].

The use of small molecule drugs to bind cytokine ligands and disrupt interactions with extracellular GAGs has been reported with FGF-dependent angiogenesis [Folkman and Shing, *Adv Exp Med Biol* 313:355-364 (1992)]. For example, the heparinoids suramin and pentosan polysulphate both inhibit angiogenesis under conditions where heparin is either ineffective or even stimulatory [Wellstein and Czubayko, *Breast Cancer Res Treat* 38:109-119 (1996)]. In the case of suramin, the anti-angiogenic capacity of the drug has also been shown to be targeted against VEGF [Waltenberger et al., *J Mol Cell Cardiol* 28:1523-1529 (1996)] which, like FGF, possesses heparin-binding domains similar to those of the chemokines. Heparin or heparin sulphate has also been shown to directly compete for GAG interactions critical for T-cell adhesion mediated by MIP-1β *in vitro* [Tanaka et al., *Nature* 361:79-82 (1993)].

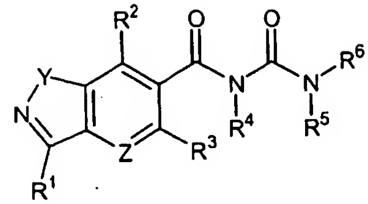
SUMMARY OF THE INVENTION

The present invention relates to compounds that inhibit MCP-1-induced chemotaxis of human monocytic cells both *in vitro* and *in vivo*. These novel MCP-1 antagonists are useful for the treatment of inflammatory diseases, especially those associated with lymphocyte and/or monocyte accumulation, such as atherosclerosis, diabetic nephropathy, inflammatory bowel disease, Crohn's disease, multiple sclerosis, nephritis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, and other chronic or acute autoimmune disorders. In addition, these compounds can be used in the treatment of allergic hypersensitivity disorders, such as asthma and allergic rhinitis, characterized by basophil activation and eosinophil recruitment.

A first embodiment of the present invention provides compounds of Formula (I) or Formula (II):



(I)



(II)

wherein

Y is O, S or N-R^7,

Z is N or C-R^8,

R^1, R^2, R^3, and R^8 are independently, hydrogen, or optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halo(lower alkyl), $-CF_3$, halogen, nitro, -CN, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-NR^9$(carboxy(lower alkyl)), $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-OC(=O)R^9$, $-SO_2R^9$, $-OSO_2R^9$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-N(C_{1-2} alkyl)$_2$, lower alkyl(optionally substituted heterocycloalkyl), alkenyl, alkynyl, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl(lower alkyl), aryl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group,

R^7 is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2R^9$, or $-SO_2NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower

alkyl, lower alkyl-N(C_{1-2} alkyl)$_2$, lower alkyl(optionally substituted heterocycloalkyl), alkenyl, alkynyl, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl(lower alkyl), aryl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are -$(CH_2)_{4-6}$- optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group,

R^4 and R^5 are independently, hydrogen, lower alkyl optionally substituted lower alkyl, optionally substituted aryl, or optionally substituted aryl(lower alkyl), or, together, are -$(CH_2)_{2-4}$-,

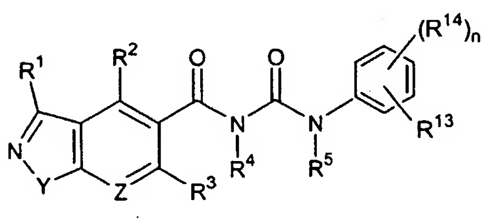
R^6 is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), -C(=O)R^{11}, -C(=O)OR^{11}, -C(=O)N$R^{11}R^{12}$, -SO_2R^{11}, or -$SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^{11} and R^{12} together are -$(CH_2)_{4-6}$-,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

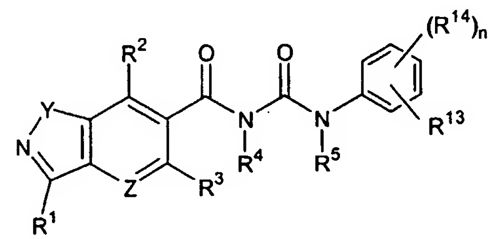
The compounds of this invention may possess one or more chiral centers, and can therefore be produced as individual stereoisomers or as mixtures of stereoisomers, depending on whether individual stereoisomers or mixtures of stereoisomers of the starting materials are used. In addition, some of the compounds of the invention are capable of further forming pharmaceutically acceptable salts and esters. The compounds of this invention may further exist in tautomeric forms and can therefore be produced as individual tautomeric forms or as mixtures of tautomeric forms. Unless indicated otherwise, the description or naming of a compound or groups of compounds is intended to

include both the individual isomers or mixtures (racemic or otherwise) of stereoisomers and their tautomeric forms. Methods for the determination of stereochemistry and the separation of stereoisomers are well known to a person of ordinary skill in the art [see the discussion in Chapter 4 of March J.: *Advanced Organic Chemistry*, 4th ed. John Wiley and Sons, New York, NY, 1992]. All of these stereoisomers and pharmaceutical forms are intended to be included within the scope of the present invention.

A second embodiment of the present invention provides compounds of Formula (Ia) or Formula (IIa):



(Ia)



(IIa)

where:

Y is O, S or N-R^7,

Z is N or C-R^8,

R^1, R^2, R^3, R^4, R^5, R^7 and R^8 are as defined in the first embodiment,

R^{13} is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), heterocycloalkyl, optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), -CF_3, halogen, nitro, -CN, -OR^{15}, -SR^{15}, -$NR^{15}R^{16}$, -C(=O)R^{15}, -C(=O)OR^{15}, -C(=O)$NR^{15}R^{16}$, -OC(=O)R^{15}, -SO_2R^{15}, -$SO_2NR^{15}R^{16}$, -$NR^{15}SO_2R^{16}$ or -NR^{15}C(=O)R^{16}, wherein R^{15} and R^{16} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, -CF_3, cycloalkyl, optionally substituted heterocycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl,

optionally substituted aryloxy, optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl) or, together, are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH or N-(C_{1-2} alkyl) group,

each R^{14} is independently selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxy, halogen, $-CF_3$, $-OR^{17}$, $-NR^{17}R^{18}$, $-C(=O)R^{18}$, $-C(=O)OR^{18}$, $-C(=O)NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently, hydrogen, lower alkyl, alkenyl, alkynyl, $-CF_3$, optionally substituted heterocycloalkyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or, together, are $-(CH_2)_{4-6}-$, optionally interrupted by one O, S, NH or N-(C_{1-2} alkyl) group, and

where n is an integer of 0 to 4,

or a pharmaceutically acceptable salt thereof as a single stereoisomer or mixture of stereoisomers.

A third embodiment of the present invention provides pharmaceutical compositions comprising pharmaceutically acceptable excipients and a therapeutically effective amount of at least one compound of this invention.

A fourth embodiment of the present invention provides methods for treating chronic or acute inflammatory or autoimmune diseases such as asthma, atherosclerosis, diabetic nephropathy, glomerulonephritis, inflammatory bowel disease, Crohn's disease, multiple sclerosis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, or a transplant rejection in mammals in need thereof, comprising the administration to such mammal of a therapeutically effective amount of at least one compound of this invention or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising the same.

A fifth embodiment of this invention provides uses of the compounds of the invention in the preparation of medicaments for the treatment of chronic or acute inflammatory or autoimmune diseases such as asthma, atherosclerosis, diabetic nephropathy, glomerulonephritis, inflammatory bowel disease, Crohn's

disease, multiple sclerosis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, or a transplant rejection.

A sixth embodiment of this invention provides a process for the preparation of the compounds of the invention or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Parameters

The following definitions apply to the description of compounds of the present invention:

"Alkyl" is a linear or branched saturated hydrocarbon radical having from 1 to 20 carbon atoms. Examples of alkyl radicals are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, dodecyl, etc.

"Lower alkyl", as in "lower alkyl," "lower alkoxy," "cycloalkyl(lower alkyl)," "aryl(lower alkyl)", or "heteroaryl(lower alkyl)", means a C_{1-10} alkyl radical. Preferred lower alkyl radicals are those having from 1 to 6 carbon atoms.

"Alkenyl" is a linear or branched hydrocarbon radical having from 2 to 20 carbon atoms and at least one carbon-carbon double bond. Examples of alkenyl radicals are: vinyl, 1-propenyl, isobutenyl, etc.

"Alkynyl" is a linear or branched hydrocarbon radical having from 2 to 20 carbon atoms and at least one carbon-carbon triple bond. Examples of alkynyl radicals are: propargyl, 1-butynyl, etc.

"Cycloalkyl" is a monovalent cyclic hydrocarbon radical having from 3 to 12 carbon atoms. Examples of cycloalkyl radicals are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

"Substituted cycloalkyl" is a monovalent cyclic hydrocarbon radical having from 3 to 12 carbon atoms, which is substituted with one, two, or three substituents each independently selected from aryl, substituted aryl, heteroaryl, halogen, $-CF_3$, nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, -NRC(=O)R′ or $-PO_3HR$, wherein R and R′ are, independently, hydrogen, lower alkyl, cycloalkyl,

aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl), and having 3 to 12 ring atoms, 1 to 5 of which are heteroatoms chosen, independently, from N, O, or S, and includes monocyclic, condensed heterocyclic, and condensed carbocyclic and heterocyclic rings (e.g. piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, etc.).

"Cycloalkyl(lower alkyl)" is a lower alkyl radical which is substituted with a cycloalkyl, as previously defined. Examples of cycloalkyl(lower alkyl) radicals are cyclopropylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl, etc.

"Heterocycloalkyl" is a monovalent cyclic hydrocarbon radical having 3 to 12 carbon ring atoms, 1 to 5 of which are heteroatoms chosen, independently, from N, O, or S, and includes monocyclic, condensed heterocyclic, and condensed carbocyclic and heterocyclic rings (e.g. piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, etc.).

"Substituted heterocycloalkyl" is a monovalent cyclic hydrocarbon radical having from 3 to 12 carbon atoms, which is substituted with one, two, or three substituents each independently selected from aryl, substituted aryl, heteroaryl, halogen, $-CF_3$ nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, -NRC(=O)R′ or $-PO_3HR$, wherein R and R′ are, independently, hydrogen, lower alkyl, cycloalkyl, aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl), and having 3 to 12 ring atoms, 1 to 5 of which are heteroatoms chosen, independently, from N, O, or S, and includes monocyclic, condensed heterocyclic, and condensed carbocyclic and heterocyclic rings (e.g. piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, etc.).

"Substituted heterocycloalkyl(lower alkyl)" is a lower alkyl radical which is substituted with a monovalent cyclic hydrocarbon radical having from 3 to 12 carbon atoms, which is substituted with one, two, or three substituents each independently selected from aryl, substituted aryl, heteroaryl, halogen, $-CF_3$ nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, -NRC(=O)R′ or $-PO_3HR$, wherein R and R′

are, independently, hydrogen, lower alkyl, cycloalkyl, aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl), and having 3 to 12 ring atoms, 1 to 5 of which are heteroatoms chosen, independently, from N, O, or S, and includes monocyclic, condensed heterocyclic, and condensed carbocyclic and heterocyclic rings (e.g. piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, etc.).

"Substituted alkyl" or "substituted lower alkyl," is an alkyl or lower alkyl radical, respectively, which is substituted with one, two, or three substituents each independently selected from aryl, substituted aryl, heteroaryl, halogen, $-CF_3$ nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, -NRC(=O)R′, or $-PO_3HR$, wherein R and R′ are, independently, hydrogen, lower alkyl, cycloalkyl, aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl).

"Halo(lower alkyl)" is a radical derived from lower alkyl containing at least one halogen substituent. Non-limiting examples of halo(lower alkyl) radicals include: $-CF_3$, C_2F_5, etc..

"Aryl", as in "aryl", "aryloxy", and "aryl(lower alkyl)", is a radical derived from an aromatic hydrocarbon containing 6 to 16 ring carbon atoms, having a single ring (*e.g.*, phenyl), or two or more condensed rings, preferably 2 to 3 condensed rings (*e.g.*, naphthyl), or two or more aromatic rings, preferably 2 to 3 aromatic rings, which are linked by a single bond (*e.g.*, biphenyl). Preferred aryl radicals are those containing from 6 to 14 carbon atoms.

"Substituted aryl" is an aryl radical which is substituted with one, two, or three substituents each independently selected from alkyl, substituted alkyl, halo(lower alkyl), halogen, nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-PO_3H_2$, $-NRSO_2R'$, -C(=O)NRR′ or -NRC(=O)R′, wherein R and R′ are, independently, hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, substituted aryl, optionally substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl). Preferred substituted aryl radicals are those substituted with one, two, or three substituents each

independently selected from the group consisting of lower alkyl, halogen, $-CF_3$, nitro, -CN, -OR, -NRR′, -C(=O)NRR′, $-SO_2OR$, $-SO_2NRR'$, $-PO_3H_2$, $-NRSO_2R'$ or -NRC(=O)R′.

"Substituted aryloxy" is an –OR radical where R is a radical derived from an aromatic hydrocarbon containing 6 to 16 ring carbon atoms, having a single ring (*e.g.*, phenyl), or two or more condensed rings, preferably 2 to 3 condensed rings (*e.g.*, naphthyl), or two or more aromatic rings, preferably 2 to 3 aromatic rings, which are linked by a single bond (*e.g.*, biphenyl), and which is substituted with one, two, or three substituents each independently selected from aryl, substituted aryl, heteroaryl, halogen, $-CF_3$, nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, -OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, -NRC(=O)R′ or $-PO_3HR$, wherein R and R′ are, independently, hydrogen, lower alkyl, cycloalkyl, aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl, or heteroaryl(lower alkyl). Preferred aryl radicals are those containing from 6 to 14 carbon atoms.

"Heteroaryl", as in "heteroaryl" and "heteroaryl(lower alkyl)", is a radical derived from an aromatic hydrocarbon containing 5 to 14 ring atoms, 1 to 5 of which are heteroatoms chosen, independently, from N, O, or S, and includes monocyclic, condensed heterocyclic, and condensed carbocyclic and heterocyclic aromatic rings (*e.g.*, thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxazolyl, indolyl, isobenzofuranyl, purinyl, isoquinolyl, pteridinyl, imidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, etc.).

"Substituted heteroaryl" is a heteroaryl radical which is substituted with one, two, or three substituents each independently selected from alkyl, substituted alkyl, halogen, CF_3, nitro, -CN, -OR, -SR, -NRR′, -C(=O)R, OC(=O)R, -C(=O)OR, $-SO_2OR$, $-OSO_2R$, $-SO_2NRR'$, $-NRSO_2R'$, -C(=O)NRR′, or -NRC(=O)R′, wherein R and R′ are, independently, hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, aryl, substituted aryl, aryl(lower alkyl), substituted aryl(lower alkyl), heteroaryl,. or heteroaryl(lower alkyl). Particularly preferred substituents on the substituted heteroaryl moiety include lower alkyl, substituted lower alkyl, halo(lower alkyl), halogen, nitro, -CN, -OR, -SR, and -NRR′.

"Aryl(lower alkyl)" is a lower alkyl radical which is substituted with an aryl, as previously defined.

"Substituted aryl(lower alkyl)" is an aryl(lower alkyl) radical having one to three substituents on either or both of the aryl and the alkyl portion of the radical.

"Heteroaryl(lower alkyl)" is a lower alkyl radical which is substituted with a heteroaryl, as previously defined.

"Substituted heteroaryl(lower alkyl)" is a heteroaryl(lower alkyl) radical having one to three substituents on the heteroaryl portion or the alkyl portion of the radical, or both.

"Lower alkoxy" is an -OR radical, where R is a lower alkyl or cycloalkyl.

"Halogen" means fluoro, chloro, bromo, or iodo.

"Stereoisomers" are compounds that have the same sequence of covalent bonds and differ in the relative disposition of their atoms in space.

"Inner salts" or "Zwitterions" can be formed by transferring a proton from the carboxyl group onto the lone pair of electrons of the nitrogen atom in the amino group.

"Tautomers" are isomeric compounds that differ from one another by interchanged positions of σ and π bonds. The compounds are in equilibrium with one another. They may also differ from one another in the position at which a hydrogen atom is attached.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients may be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous.

"Pharmaceutically acceptable salts and esters" means any salt and ester that is pharmaceutically acceptable and has the desired pharmacological properties. Such salts include salts that may be derived from an inorganic or organic acid, or an inorganic or organic base, including amino acids, which is not toxic or undesirable in any way. Suitable inorganic salts include those formed with the alkali metals, *e.g.* sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such

as the amine bases, *e.g.* ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (*e.g.* hydrochloric and hydrobromic acids) and organic acids (*e.g.* acetic acid, citric acid, maleic acid, and the alkane and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds, *e.g.* C1-6 alkyl esters. When there are two acidic groups present, a pharmaceutically acceptable salt or ester may be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly, where there are more than two acidic groups present, some or all of such groups can be salified or esterified.

"Therapeutically effective amount" means that amount which, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease in a mammal includes:

(1) Preventing the disease from occurring in a mammal which may be predisposed to the disease but does not yet experience or display symptoms of the disease;

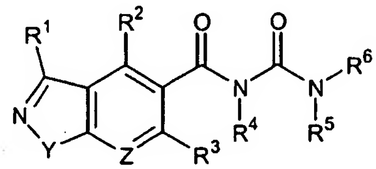
(2) Inhibiting the disease, *i.e.*, arresting its development, or

(3) Relieving the disease, *i.e.*, causing regression of the disease.

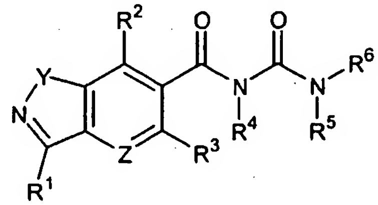
"Disease" includes any unhealthy condition of an animal (which includes human and non-human mammals), including particularly various forms of inflammatory illnesses or diseases, such as asthma, atherosclerosis, diabetic nephropathy, glomerulonephritis, inflammatory bowel disease, Crohn's disease, multiple sclerosis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, immune disorders, and transplant rejection.

The Compounds and Their Pharmaceutically Acceptable Salts

The first embodiment of the present invention provides compounds of Formula (I) and Formula (II):



(I)



(II)

wherein Y, Z, and R^1 to R^{12} are as defined above.

Where R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group, examples include piperazinyl, 4-methylpiperazinyl, 4-morpholyl, and hexahydropyrimidyl.

Preferably, Y is O or $N\text{-}R^7$.

Preferably, R^1 is hydrogen, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halogen, $-OR^9$, $-NR^9R^{10}$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2NR^9R^{10}$, or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1-2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), aryl(lower alkyl), optionally substituted aryl, heteroaryl, or heteroaryl(lower alkyl).

More preferably, R^1 is optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halogen, $-OR^9$, $-NR^9R^{10}$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2NR^9R^{10}$, or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1-2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), aryl(lower alkyl), optionally substituted aryl, heteroaryl, or heteroaryl(lower alkyl).

Preferably, R^2 is hydrogen, optionally substituted lower alkyl, cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halogen, $-OR^9$, $-NR^9$(carboxy(lower alkyl)), $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2NR^9R^{10}$, or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1-2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

More preferably, R^2 is optionally substituted lower alkyl, cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halogen, $-OR^9$, $-NR^9$(carboxy(lower alkyl)), $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2NR^9R^{10}$, or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1-2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

Preferably, R^3 is hydrogen, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halo(lower alkyl), halogen, $-OR^9$, $-NR^9R^{10}$, $-C(=O)OR^9$, or $-C(=O)NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1-2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

More preferably, R^3 is optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halo(lower alkyl), halogen, $-OR^9$, $-NR^9R^{10}$, $-C(=O)OR^9$, or $-C(=O)NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-N(C_{1-2} alkyl)$_2$, lower alkyl(optionally substituted heterocycloalkyl), optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

Preferably, R^7 is hydrogen, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-SO_2R^9$, or $-SO_2NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-N(C_{1-2} alkyl)$_2$, alkenyl, alkynyl, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, heteroaryl, or heteroaryl(lower alkyl).

Preferably, R^8 is hydrogen, optionally substituted lower alkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryl(lower alkyl), halo(lower alkyl), $-CF_3$, halogen, $-OR^9$, $-NR^9R^{10}$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)NR^9R^{10}$, $-OC(=O)R^9$, $-SO_2R^9$, $-SO_2NR^9R^{10}$, $-NR^9SO_2R^{10}$ or $-NR^9C(=O)R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-N(C_{1-2} alkyl)$_2$, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

Preferably, R^4 and R^5 are independently, hydrogen or lower alkyl, or together are $-(CH_2)_{2-4}-$. More preferably, R^4 and R^5 are independently, hydrogen or lower alkyl.

Preferably, R^6 is hydrogen, optionally substituted lower alkyl, alkenyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl,

optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-SO_2R^{11}$, or $-SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently, hydrogen, optionally substituted lower alkyl, cycloalkyl, cycloalkyl(lower alkyl), aryl, heteroaryl, heteroaryl(lower alkyl), or R^{11} and R^{12} together are $-(CH_2)_{4\text{-}6}-$.

A particular preferred "substituted aryl" is a phenyl group substituted with a R^{13} and optionally substituted with up to four R^{14}s, where R^{13} and R^{14} are defined with respect to formulae Ia and IIa.

The above-listed preferences equally apply for the compounds of Formulae Ia and IIa, below.

In a more preferred version of the first embodiment of the invention,

Y is $N\text{-}R^7$ and Z is N,

R^1 is lower alkyl,

R^4 and R^5 are hydrogen, and

R^6 is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl, optionally substituted aryl, aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-SO_2R^{11}$, or $-SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^{11} and R^{12} together are $-(CH_2)_{4\text{-}6}-$,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

More preferably still, R^2 is $-NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1\text{-}2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), alkenyl, alkynyl, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), benzyl, optionally substituted aryl, optionally substituted aryloxy,

heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted C_{1-2} alkyl) group.

In another more preferred version of the first embodiment of the invention,

Y is $N-R^7$ and Z are N,

R^1 and R^8 are lower alkyl,

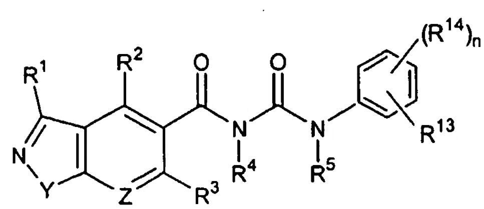
R^2 is $-NR^9R^{10}$,

R^4 and R^5 are hydrogen, and

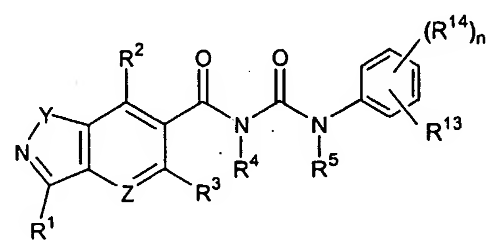
R^6 is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted heterocycloalkyl, optionally substituted aryl, aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-SO_2R^{11}$, or $-SO_2NR^{11}R^{12}$, wherein R^{11} and R^{12} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^{11} and R^{12} together are $-(CH_2)_{4-6}-$,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

The second embodiment of the present invention provides compounds of Formula (Ia) or Formula (IIa):



(Ia)



(IIa)

wherein:

Y is O, S or N-R^7,

Z is N or C-R^8,

R^1, R^2, R^3, R^4, R^5, R^7 and R^8 are as defined in the first embodiment,

R^{13} is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), heterocycloalkyl, optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), -CF_3, halogen, nitro, -CN, -OR^{15}, -SR^{15}, -$NR^{15}R^{16}$, -$C(=O)R^{15}$, -$C(=O)OR^{15}$, -$C(=O)NR^{15}R^{16}$, -$OC(=O)R^{15}$, -SO_2R^{15}, -$SO_2NR^{15}R^{16}$, -$NR^{15}SO_2R^{16}$ or -$NR^{15}C(=O)R^{16}$, wherein R^{15} and R^{16} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, -CF_3, cycloalkyl, optionally substituted heterocycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), or, together, are -$(CH_2)_{4\text{-}6}$- optionally interrupted by one O, S, NH or N-($C_{1\text{-}2}$ alkyl) group,

each R^{14} is independently selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxy, halogen, -CF_3, -OR^{17} -$NR^{17}R^{18}$, -$C(=O)R^{18}$, -$C(=O)OR^{18}$, -$C(=O)NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently, hydrogen, lower alkyl, alkenyl, alkynyl, -CF_3, optionally substituted heterocycloalkyl, cycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or, together, are -$(CH_2)_{4\text{-}6}$-, optionally interrupted by one O, S, NH or N-($C_{1\text{-}2}$ alkyl) group, and

where n is an integer of 0 to 4,

or a pharmaceutically acceptable salt thereof as a single stereoisomer or mixture of stereoisomers.

Wherein R^{13} is $-OR^{15}$, and R^{15} is optionally substituted lower alkyl, it may, for example, be optionally substituted with $-C(=O)OR^{19}$, wherein R^{19} is hydrogen or lower alkyl.

Where R^9 and R^{10} together are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH or N-(C_{1-2} alkyl) group, examples include piperazinyl, 4-methylpiperazinyl, morpholyl, and hexahydropyrimidyl.

n is a stereocompatible integer of 0 to 4. The term "stereocompatible" limits the number of substituents permissible by available valences in accordance with space requirements of substituents, among other.

Preferably, R^{13} is hydrogen, optionally substituted lower alkyl, alkenyl, heterocycloalkyl, optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), $-CF_3$, halogen, nitro, -CN, $-OR^{15}$, $-SR^{15}$, $-NR^{15}R^{16}$, $-C(=O)R^{15}$, $-C(=O)OR^{15}$, $-C(=O)NR^{15}R^{16}$, $-OC(=O)R^{15}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, or $-NR^{15}C(=O)R^{16}$, wherein R^{15} and R^{16} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, cycloalkyl, optionally substituted heterocycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl) or, together, are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH or N-(C_{1-2} alkyl) group.

More preferably, R^{13} is optionally substituted lower alkyl, alkenyl, heterocycloalkyl, optionally substituted aryl, optionally substituted aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), $-CF_3$, halogen, nitro, -CN, $-OR^{15}$, $-SR^{15}$, $-NR^{15}R^{16}$, $-C(=O)R^{15}$, $-C(=O)OR^{15}$, $-C(=O)NR^{15}R^{16}$, $-OC(=O)R^{15}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, or $-NR^{15}C(=O)R^{16}$, wherein R^{15} and R^{16} are independently, hydrogen, optionally substituted lower alkyl, alkenyl, cycloalkyl, optionally substituted heterocycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl) or, together, are $-(CH_2)_{4-6}-$ optionally interrupted by one O, S, NH or N-(C_{1-2} alkyl) group.

Preferably, R^{14} is independently selected from optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, hydroxy,

halogen, $-CF_3$, $-OR^{17}$ $-NR^{17}R^{18}$, $-C(=O)R^{18}$, $-C(=O)OR^{18}$, $-C(=O)NR^{17}R^{18}$, wherein R^{17} and R^{18} are, independently, hydrogen, lower alkyl, alkenyl, or optionally substituted aryl.

Preferably, where R^{13} is not hydrogen, n is an integer of 1 to 2. More preferably, where R^{13} is not hydrogen, n is 1.

In another more preferred version of the second embodiment of the invention,

Y is $N\text{-}R^7$ and Z is N,

R^1 is lower alkyl,

R^2 is $-NR^9R^{10}$, wherein R^9 and R^{10} are independently, hydrogen, optionally substituted lower alkyl, lower alkyl-$N(C_{1\text{-}2}$ alkyl$)_2$, lower alkyl(optionally substituted heterocycloalkyl), alkenyl, alkynyl, optionally substituted cycloalkyl, cycloalkyl(lower alkyl), benzyl, optionally substituted aryl, optionally substituted aryloxy, heteroaryl, heteroaryl(lower alkyl), or R^9 and R^{10} together are $-(CH_2)_{4\text{-}6}-$ optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-(carboxy(lower alkyl)) or N-(optionally substituted $C_{1\text{-}2}$ alkyl) group such as piperazinyl, 4-methylpiperazinyl, 4-morpholyl, hexahydropyrimidyl, and

R^{13} is hydrogen, optionally substituted lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(lower alkyl), heterocycloalkyl, optionally substituted aryl, aryl(lower alkyl), optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl), halo(lower alkyl), $-CF_3$, halogen, nitro, -CN, $-OR^{15}$, $-SR^{15}$, $-NR^{15}R^{16}$, $-C(=O)R^{15}$, $-C(=O)OR^{15}$, $-C(=O)NR^{15}R^{16}$, $-OC(=O)R^{15}$, $-SO_2R^{15}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}SO_2R^{16}$ or $-NR^{15}C(=O)R^{16}$, wherein R^{15} and R^{16} are independently, hydrogen, lower alkyl, alkenyl, alkynyl, $-CF_3$, cycloalkyl, optionally substituted heterocycloalkyl, cycloalkyl(lower alkyl), optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, optionally substituted heteroaryl(lower alkyl) or R^{15} and R^{16} together are $-(CH_2)_{4\text{-}6}-$ optionally interrupted by one O, S, NH or N-($C_{1\text{-}2}$ alkyl) group.

More preferably still, R^4 and R^5 are hydrogen.

Most preferably, independently,

1. Y is O, and R^1 is lower alkyl.
2. Y is N-R^7, R^7 are hydrogen or lower alkyl, and R^1 is lower alkyl.
3. Y -s N-R^7, and R^7 is methyl.
4. Z is N.
5. Z is C-R^8, and R^8 is hydrogen.
6. R^2 and R^3 are independently selected from hydrogen, lower alkyl, halogen, OR^9, $-NR^9R^{10}$, where R^9 and R^{10} are independently lower alkyl, substituted lower alkyl, or substituted aryl, or R^9 and R^{10} together are $-(CH_2)_{4\text{-}6}$- optionally interrupted by one O, S, NH, N-(aryl), N-(aryl(lower alkyl)), N-COOH, N-(carboxy(lower alkyl)) or N-(optionally substituted $C_{1\text{-}2}$ alkyl) group.
7. R^{13} is independently selected from halogen, optionally substituted aryl, $-CF_3$, $-CH_3$, -CN, $-OR^{15}$, $-C(=O)R^{15}$, $-C(=O)OR^{15}$, $-C(=O)NR^{15}R^{16}$, or $-CO_2H$.
8. R^{14} is independently selected from halogen, optionally substituted lower alkyl, $-CF_3$, $-OR^{17}$, aryl, heteroaryl, $-NR^{17}R^{18}$, $-C(=O)R^{17}$, $-C(=O)OR^{17}$, $-C(=O)NR^{17}R^{18}$, or $-CO_2H$, where R^{17} and R^{18} are, independently, lower alkyl, substituted lower alkyl, or substituted aryl, or, together, are $-(CH_2)_{4\text{-}6}$- optionally interrupted by one O, S, NH or N-($C_{1\text{-}2}$ alkyl) group.
9. Z is N, R^2 is 4-methylpiperazinyl, R^{13} is 3-CF_3, and R^{14} is 4-F.

The preferred compounds of the invention are listed in Tables 1-4 below.

The compounds of this invention may possess one or more chiral centers, and can therefore exist as individual stereoisomers or as mixtures of stereoisomers. In such cases, all stereoisomers also fall within the scope of this invention. The compounds of this invention may also exist in various tautomeric forms, and in such cases, all tautomers also fall within the scope of this invention. The invention compounds include the individually isolated stereoisomers and tautomers as well as mixtures of such stereoisomers and their tautomers.

Some of the compounds of Formula (I) and Formula (II) are capable of further forming pharmaceutically acceptable salts and esters. All of these forms are included within the scope of the present invention.

Pharmaceutically acceptable base addition salts of the compounds of Formula (I) and Formula (II) include salts which may be formed when acidic protons present in the parent compound are capable of reacting with inorganic or organic bases. Typically, the parent compound is treated with an excess of an alkaline reagent, such as hydroxide, carbonate, or alkoxide, containing an appropriate cation. Cations such as Na^+, K^+, Ca^{2+}, and NH_4^+ are examples of cations present in pharmaceutically acceptable salts. The Na^+ salts are especially useful. Acceptable inorganic bases, therefore, include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide. Salts may also be prepared using organic bases, such as choline, dicyclohexylamine, ethylenediamine, ethanolamine, diethanolamine, triethanolamine, procaine, *N*-methylglucamine, and the like [for a nonexclusive list see, for example, Berge et al., "Pharmaceutical Salts," *J. Pharma. Sci.* 66:1 (1977)]. The free acid form may be regenerated by contacting the base addition salt with an acid and isolating the free acid in the conventional manner. The free acid forms can differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents.

Pharmaceutically acceptable acid addition salts of the compounds of Formula (I) and Formula (II) include salts which may be formed when the parent compound contains a basic group. Acid addition salts of the compounds are prepared in a suitable solvent from the parent compound and an excess of a non-toxic inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, or a non-toxic organic acid such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, salicylic acid, *p*-toluenesulfonic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, lactic acid, *o*-(4-hydroxy-benzoyl)benzoic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, camphorsulfonic acid, 4-methyl-bicyclo[2.2.2.]oct-2-ene-1-carboxylic acid, glucoheptonic acid, gluconic

acid, 4,4'-methylenebis(3-hydroxy-2-naphthoic)acid, 3-phenylpropionic acid, trimethylacetic acid, *tert*-butylacetic acid, laurylsulfuric acid, glucuronic acid, glutamic acid, 3-hydroxy-2-naphthoic acid, stearic acid, muconic acid, and the like. The free base form may be regenerated by contacting the acid addition salt with a base and isolating the free base in the conventional manner. The free base forms can differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents.

Also included in the embodiment of the present invention are salts of amino acids such as arginate and the like, gluconate, and galacturonate [see Berge, *supra* (1977)].

Some of the compounds of the invention may form inner salts or Zwitterions.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms, and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention may also exist in one or more solid or crystalline phases or polymorphs, the variable biological activities of such polymorphs or mixtures of such polymorphs are also included in the scope of this invention.

Pharmaceutical Compositions

A third embodiment of the present invention provides pharmaceutical compositions comprising pharmaceutically acceptable excipients and a therapeutically effective amount of at least one compound of this invention.

Pharmaceutical compositions of the compounds of this invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulations are especially suitable for parenteral administration but may also be used for oral

administration. It may be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acacia, polyethylene glycol, mannitol, sodium chloride, or sodium citrate.

Alternatively, these compounds may be encapsulated, tableted, or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, alcohols, or water. Solid carriers include starch, lactose, calcium sulfate, dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar, or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit.

The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing, and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

Some specific examples of suitable pharmaceutical compositions are described in Examples 27-29.

Typically, a pharmaceutical composition of the present invention is packaged in a container with a label indicating the use of the pharmaceutical composition in the treatment of a disease such as asthma, atherosclerosis, diabetic nephropathy, glomerulonephritis, inflammatory bowel disease, Crohn's disease, multiple sclerosis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, and transplant rejection, or a chronic or acute immune disorder, or a combination of any of these disease conditions.

Methods of Use:

A fourth embodiment of the present invention provides a method for treating a chronic or acute inflammatory disease such as asthma, atherosclerosis, diabetic nephropathy, glomerulonephritis, inflammatory bowel disease, Crohn's disease, multiple sclerosis, pancreatitis, pulmonary fibrosis, psoriasis, restenosis, rheumatoid arthritis, or a chronic or acute immune disorder, or a transplant rejection in mammals in need thereof, comprising the administration to such mammal of a therapeutically effective amount of at least one compound of general Formula (I) and Formula (II) or pharmaceutically acceptable salts and esters thereof.

The compounds of the present invention inhibit chemotaxis of a human monocytic cell line (THP-1 cells) induced by human MCP-1 *in vitro*. This inhibitory effect has also been observed *in vivo*. Indeed, the compounds have been shown to reduce monocyte infiltration in a thioglycollate-induced inflammation model in mice.

The compounds of the present invention have been found to prevent the onset or ameliorate symptoms in several animal models of inflammation. For example, the compounds inhibited recruitment of monocytes into the glomeruli in an anti-Thy-1 antibody-induced model of nephritis; reduced paw swelling in a rat model of adjuvant arthritis; inhibited neointimal hyperplasia after balloon injury in a rat model of restenosis, and reduced the amount of lesion of the aortic sinus in an apoE-deficient mouse model of atherosclerosis.

The ability of the compounds of this invention to block the migration of monocytes and prevent or ameliorate inflammation, which is demonstrated in the specific examples, indicates their usefulness in the treatment and management of disease states associated with aberrant leukocyte recruitment.

The use of the compounds of the invention for treating inflammatory and autoimmune disease by combination therapy may also comprise the administration of the compound of the invention to a mammal in combination with common anti-inflammatory drugs, cytokines, or immunomodulators.

The compounds of this invention are thus used to inhibit leukocyte migration in patients which require such treatment. The method of treatment

comprises the administration, orally or parenterally, of an effective quantity of the chosen compound of the invention, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are generally selected from the range of 0.01 to 1000 mg/kg, preferably 0.01 to 100 mg/kg, and more preferably 0.1 to 50 mg/kg, but the range will be readily determined by one skilled in the art depending on the route of administration, age, and condition of the patient. These dosage units may be administered one to ten times daily for acute or chronic disease. No unacceptable toxicological effects are expected when compounds of the invention are used in accordance with the present invention.

The invention compounds may be administered by any route suitable to the subject being treated and the nature of the subject's condition. Routes of administration include, but are not limited to, administration by injection, including intravenous, intraperitoneal, intramuscular, and subcutaneous injection, by transmucosal or transdermal delivery, through topical applications, nasal spray, suppository and the like, or may be administered orally. Formulations may optionally be liposomal formulations, emulsions, formulations designed to administer the drug across mucosal membranes or transdermal formulations. Suitable formulations for each of these methods of administration may be found in, for example, "Remington: The Science and Practice of Pharmacy", A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, PA.

Examples:

The following Examples serve to illustrate the preparation, properties, and therapeutic applications of the compounds of this invention. These Examples are not intended to limit the scope of this invention, but rather to show how to prepare and use the compounds of this invention.

Preparation of the Compounds of the Invention: General Procedures

The following general procedures may be employed for the preparation of the compounds of the present invention.

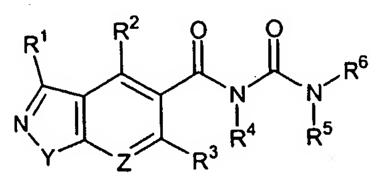
The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as the Aldrich Chemical

Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or are prepared by methods well known to a person of ordinary skill in the art, following procedures described in such references as Fieser and Fieser's *Reagents for Organic Synthesis*, vols. 1-17, John Wiley and Sons, New York, NY, 1991; *Rodd's Chemistry of Carbon Compounds*, vols. 1-5 and supps., Elsevier Science Publishers, 1989; Organic Reactions, vols. 1-40, John Wiley and Sons, New York, NY, 1991; March J.: *Advanced Organic Chemistry*, 4th ed., John Wiley and Sons, New York, NY; and Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989.

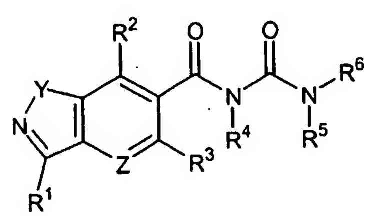
In some cases, protective groups may be introduced and finally removed. For example, suitable protective groups for amino, hydroxy, and carboxy groups are described in Greene et al., *Protective Groups in Organic Synthesis*, Second Edition, John Wiley and Sons, New York, 1991. Activation of carboxylic acids can be achieved by using a number of different reagents as described in Larock: *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989.

The starting materials, intermediates, and compounds of this invention may be isolated and purified using conventional techniques, including precipitation, filtration, distillation, crystallization, chromatography, and the like. The compounds may be characterized using conventional methods, including physical constants and spectroscopic methods.

Generally, a compound of formula I or formula II may be prepared as



(I)

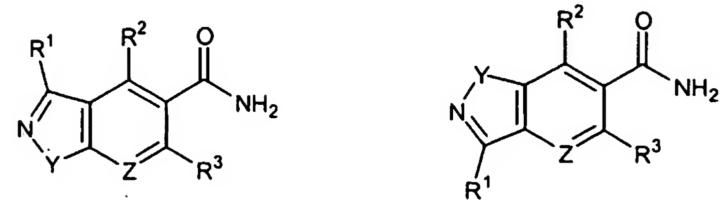


(II)

follows:

wherein Y, Z, and R^1 - R^6 are as defined in the first embodiment, said process comprising:

(a) contacting a compound of formula Ib or IIb



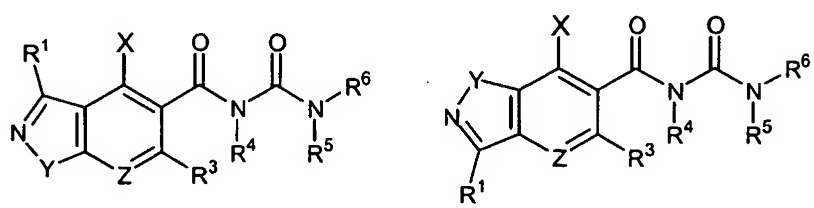
(Ib) (IIb)

with a compound of the formula

$$R^6—N=C=O$$

under conditions sufficient to produce a compounds of formula I or formula II, wherein R^4 and R^5 are both H; or

(b) contacting a compound of formula Ic or formula IIc



(Ic) (IIc)

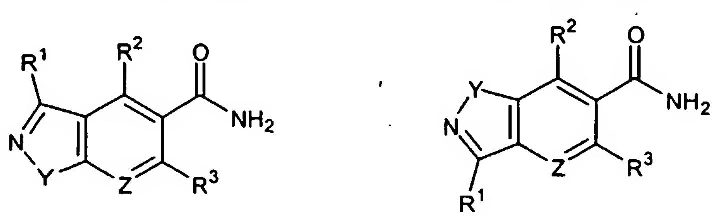
wherein X is halogen, nitro, -CN, or -OR^9,

with a compound of the formula

R^2-H,

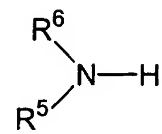
under conditions sufficient to produce a compound of formula I or formula II; or

(c) contacting a compound of formula Ib or formula IIb



(Ib) (IIb)

with a haloformylation reagent and a compound of the formula



under conditions sufficient to produce a compound of formula I or formula II, wherein R^4 is H; or

(d) elaborating substituents of a compound of formula I or formula II in a manner known *per se*; or

(e) reacting the free base of a compound of formula I or formula II with an acid to give a pharmaceutically acceptable addition salt; or

(f) reacting an acid addition salt of a compound of formula I or formula II with a base to form the corresponding free base; or

(g) converting a salt of a compound of formula I or formula II to another pharmaceutically acceptable salt of a compound of Formula I or II; or

(h) resolving a racemic mixture of any proportions of a compound of formula I or formula II to yield a stereoisomer thereof.

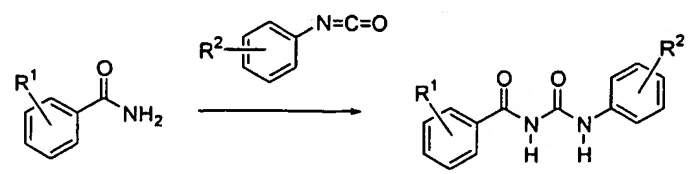
Step (a), above, may be carried out in the presence of an organic solvent or a mixture of solvents at elevated temperatures. Said organic solvent may be toluene, and the reaction may be carried out under refluxing conditions.

Step (b), above, may be carried out using the salt of the compound of the formula R^2-H in an inorganic solvent. Said salt may be the lithium, sodium, or potassium salt.

Step (c), above, may be carried out in an organic solvent or a mixture of solvents at elevated temperatures. The haloformylation reagent may be a compound of the formula A-(CO)-B wherein A and B are, independently, suitable leaving groups such as halogens, -COCl, -COBr and the like. The haloformylation agent and organic solvent employed in step (c) may be oxalyl chloride and THF, respectively, and the ensuing reaction may be heated to above 50°C.

The compounds of the invention can further be synthesized as shown in the following examples. These examples are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these examples can be made and will be suggested to a person of ordinary skill in the art having regard to this disclosure.

Procedure A:

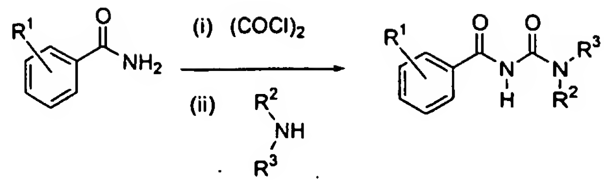


Acylurea compounds of the present invention may be prepared starting with an aryl carboxamide and an isocyanate. Carboxamide and isocyanate starting materials may be purchased from various different commercial sources, such as, for example the Aldrich Chemical Company, *supra*, or they may be prepared from standard procedures known in the art for preparing these compounds, such as the procedures described in the above-cited references. The isocyanates may also be prepared according to the procedures described in the example below. Typically, an aryl carboxamide is treated with an aryl isocyanate in an organic solvent or mixtures of suitable organic solvents. Preferably, the organic solvent is toluene. The carboxamide and the isocyanate may be combined as solutions or suspensions, depending on the solubilities of the compounds in the selected solvent. The carboxamide and the isocyanate may be added in a stoichiometric ratio (1:1), or a slight excess of the isocyanate may be used, for example between 1.01 fold and 2 fold excess, but typically about 1.01 to about 1.2 fold excess. Typically, the isocyanate is added to a suspension of the carboxamide in toluene, and the resulting mixture is heated until the reaction is determined to be complete. The reaction mixture may be heated at about 10 °C to about 150 °C, preferably at about 40 °C to about 120 °C under an inert atmosphere such as nitrogen, or the reaction mixture may be maintained at the refluxing temperature of the mixture. The reaction may be allowed to proceed to completion in about 10 minutes to 24 hours. Preferably,

the reaction is heated to reflux until the reaction is complete, over about 6 to 24 hours.

Upon cooling of the reaction mixture, the resulting precipitated acylureas may be isolated by conventional techniques. Typically, the product is isolated by filtration. The precipitated solid may be filtered, washed with a solvent or a series of solvents, and isolated without further purification. Preferably, the precipitated acylureas may be washed with a combination of toluene, methanol and then with ether, and the product may be dried under vacuum. If desired, the acylureas may be further purified using conventional techniques, such as by crystallization using conventional methods known in the art. Optionally, acylureas prepared according to this procedure may be converted to the corresponding salts prior to isolation and/or purification, or after crystallization.

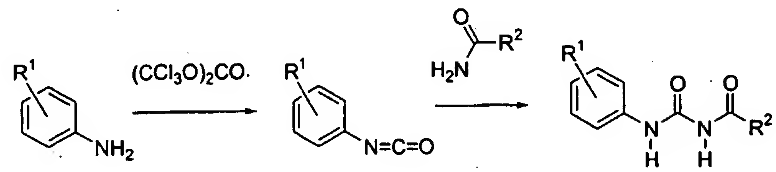
Procedure B:



Acylureas may also be prepared from the condensation of an aryl carboxamide with an amine. The carboxamide may be prepared from the corresponding carboxylic acid or may be obtained from commercial sources. Depending on the desired substitution of the amine, optionally, the amine may be substituted where one substituted group is an amine protecting group such that the protecting group may be removed in a subsequent step if desired. In the first step of the process, a carboxamide mixture in a suitable aprotic solvent is treated with a haloformylation reagent to form the corresponding carboxamide carbonylchloride derivative. Typically, the aprotic solvent is dichloromethane, toluene, 2-methyltetrahydrofuran or THF, and the haloformylation reagent is oxalyl chloride. Preferably, the aprotic solvent is THF. Oxalyl chloride is preferably present in an excess, for example between 1.1 to 3.0 equivalents, typically about 1.5 equivalent over the carboxamide. The reaction is generally performed under an inert atmosphere where the mixture is heated to 50 °C to 175 °C for 15 minutes to 24 hours until the reaction is deemed complete. Typically, the reaction is heated to reflux over 2 to 16 hours under nitrogen, and then cooled to room temperature. The solvent is removed *in vacuo* by rotoevaporation or distillation, and the resulting carboxamide carbonylchloride is then condensed with a primary or secondary amine. Condensation with the amine may be performed by the addition of a solution of the amine in an aprotic solvent, such as THF, under an inert atmosphere, at a temperature between 0 °C and 20 °C, preferably between 0 °C and 5 °C. If the chloroformylation and the subsequent condensation reaction is performed in the same solvent, the solvent removal step may be eliminated. Preferably, the reaction is performed at 0 °C to 5 °C for 1 to 24 hours, until the reaction is complete. The solvent is removed by concentration under reduced pressure, and the acylurea can be

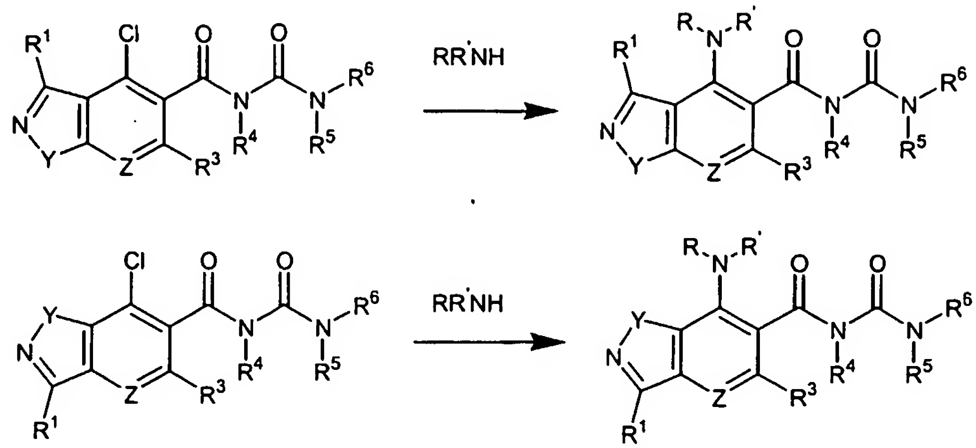
isolated by conventional techniques such as filtration and washing of the crude product with a solvent, followed by drying under vacuum.

Procedure C:



The preparation of the acylureas may also be performed starting with an amine or aniline derivative through a condensation reaction with a phosgene equivalent, followed by a condensation reaction with the carboxamide. Typically, a solution of an aniline or aniline derivative and triphosgene in tetrachloroethane or other suitable organic solvent is combined and stirred at 25 °C to 80 °C under an inert atmosphere for 2 to 12 hours until the reaction is complete. The solvent is removed under reduced pressure and the residue is dissolved in an aprotic solvent, such as toluene, and the resulting mixture is treated with a carboxamide. The mixture is heated to about 50 °C to 150 °C, preferably from about 75 °C to 115 °C. Preferably, the reaction mixture is heated to reflux for 2 to 24 hours until the reaction is complete, and allowed to cool to room temperature. The precipitated solid is isolated by conventional techniques such as filtration. The filtered solid is then washed with a suitable solvent or mixtures of solvents. Typically, the solid is washed with toluene, methanol and then ether, and the washed product is dried *in vacuo* to give the corresponding acylurea.

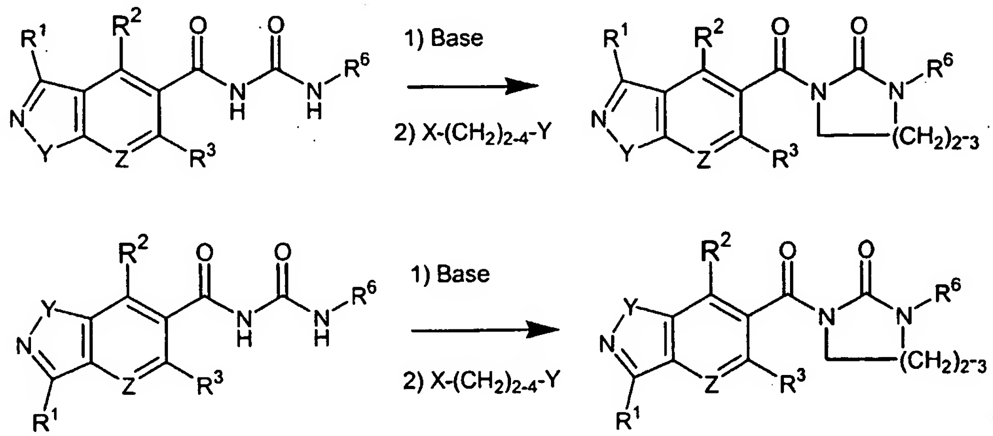
Procedure D:



Amine substituted aryl acyl ureas of the present invention may be prepared starting from the corresponding aryl halide acyl ureas by the reaction of the aryl halide with an amine. Preferably, the aryl halide is an aryl chloride, which can be prepared from one or more of the above described procedures or from standard procedures known in the art for preparing these compounds. Typically, the acyl urea is dissolved in an organic solvent or a mixture of suitable organic solvents. Preferably, the organic solvent is tetrahydrofuran. The acyl urea and the amine may be combined as solutions or suspensions, depending on the solubilities of the compounds in the selected solvent or solvent mixtures. The acyl urea and the amine may be added in a stoichiometric ratio (1:1) , or a slight excess of the amine may be used, for example, between 1.01 fold and 20 fold excess, but typically about 1.01 to about 10 fold excess. Typically, the amine is added to the acyl urea in tetrahydrofuran and the resulting mixture is stirred at about 0 °C to refluxing temperatures of the solvent, preferably at about 10 °C to about 50 °C, most preferably at about room temperatures under an inert atmosphere such as nitrogen. The reaction mixture is maintained at the reaction temperatures until the reaction proceeds to completion. The reaction may be allowed to proceed to completion in about 10 minutes to 48 hours. Preferably, the reaction is stirred at room temperature for about 5 hours. When the reaction is deemed complete, the resulting product may be isolated by conventional

techniques. Typically, the solvent and excess amine may be removed by evaporation under reduced pressure, and the residue is suspended in a solvent. Preferably, the solvent is water. The suspension or solid may be filtered and washed with water or a suitable solvent, and then isolated and dried using conventional methods.

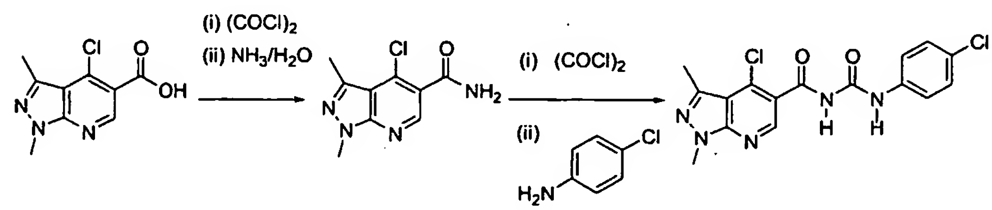
Procedure E:



Cyclic acyl ureas of the present invention may be prepared according to methods known in the art. One method comprises the alkylation of the acyl urea nitrogens with an alkylating agent generically represented above as X-$(CH_2)_{2\text{-}4}$-Y, where X and Y are leaving groups, and may be the same or different. Leaving groups known in the art include halides, methanesulfonates, trifluoromethanesulfonates, p-toluenesulfonates, p-bromotoluenesulfonate, p-nitrobenzenesulfonates and the like. Representative alkylating agents include 1,2-dibromoethane, 1,3-dibromoethane, 1,3-dibromopropane, and the corresponding sulfonates and mixed halosulfonates. Typically, the acyl urea is treated with a base in an organic solvent or mixtures of solvents. Preferably, the base is an inorganic base such as sodium hydride, or an organic base such as dimethyl sulfoxide and sodium hydride. Preferably, the solvent is a polar, aprotic solvent such as tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, glycols, or mixtures of such solvents. Typically, a solution or suspension of the acyl urea is slowly added to the base in an organic solvent at about 0 °C to about 25 °C,

and the resulting mixture is stirred for about 10 minutes to about 5 hours, preferably about 30 minutes. The alkylating agent is added and the mixture is stirred until the reaction is deemed complete. Alkylation of both urea nitrogens may be accomplished in a single step, or may be accomplished sequentially in a two step procedure be exposing the partially alkylated product with the same or different base. The reaction is then quenched with a solvent, preferably water, and the mixture is extracted multiple times with an organic solvent. Preferably, the extracting solvent is dichloromethane. The combined organic extracts are washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford the product, which may be purified using standard conditions known in the art. Purification may be performed by silica gel chromatography in a mixture of organic solvents, such as ethyl acetate and petroleum ether.

<u>**Example 1**</u>: Synthesis of *N*-(4-Chloro-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-chlorophenyl)amino]carbonyl}carboxamide (<u>**39**</u>).

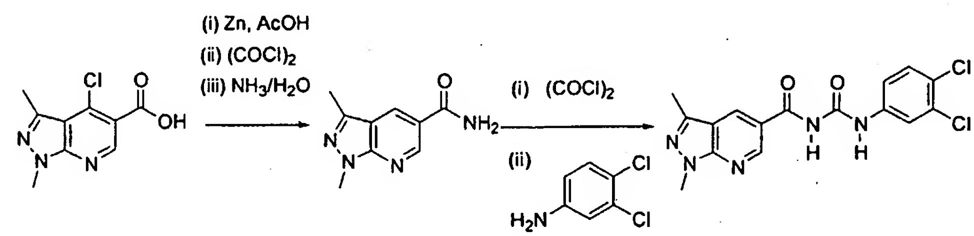


Oxalyl chloride (4.5 mL of a 2M solution in dichloromethane) was added dropwise to a stirred suspension of 4-chloro-1,3-dimethylpyrazolo [5,4-b]pyridine-5-carboxylic acid (0.98 g) in anhydrous dichloromethane (14 mL), followed by 4 drops of *N,N*-dimethylformamide (DMF). After the evolution of gas subsided, 4 more drops of DMF were added, and this operation was repeated three more times. The mixture was stirred at room temperature for 45 min, filtered to remove trace amounts of insoluble material, and the solvent evaporated under reduced pressure. The residue was dried under high vacuum for 1 h, cooled in an ice-bath, and treated with ammonium hydroxide (28% NH_3 in water, 20 mL) (*Caution! exothermic reaction*). The mixture was stirred at 0 °C for 30 min, and at room temperature for an additional 1 h. The solid was

collected by filtration, washed with water, and dried under vacuum to give the carboxamide as a white powder.

Oxalyl chloride (1.4 mL of a 2M solution in dichloromethane) was added dropwise to a suspension of 4-chloro-1,3-dimethylpyrazolo[5,4-b] pyridine-5-carboxamide (0.41 g) in anhydrous dichloromethane (5 mL). The mixture was heated at reflux for 15 h, and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in anhydrous THF (6 mL). An aliquot of this solution (1.5 mL) was added dropwise to an ice-cooled solution of 4-chloroaniline (57 mg) in anhydrous THF (2 mL). The ice-bath was removed and the mixture was stirred at room temperature for 1.5 h. The precipitated solid was collected by filtration, washed with dichloromethane and methanol, and dried under high vacuum to afford *N*-(4-Chloro-1,3-dimethyl-pyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-chlorophenyl) amino]carbonyl}carboxamide as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (s, 3H), 4.02 (s, 3H), 7.42 (d, 2H, J=8.7 Hz), 7.64 (d, 2H, J=8.7 Hz), 8.69 (s, 1H), 10.47 (s, 1H), 11.37 (s, 1H). MS (API-CI) m/z 340, 342, 344.

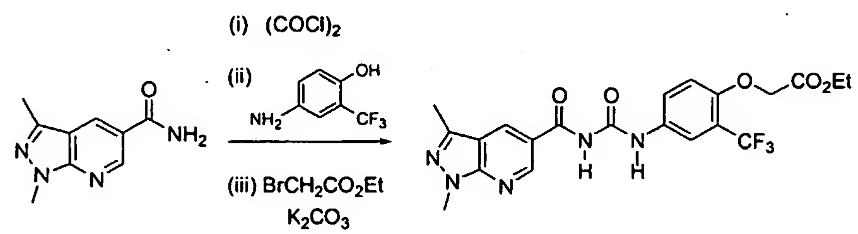
<u>Example 2</u>: Preparation of *N*-{[(3,4-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl) carboxamide (<u>2</u>).



A suspension of 4-chloro-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxylic acid (2.00 g) and zinc dust (1.74 g) in acetic acid (40 mL) was heated at 80 °C for 1.5 h. The mixture was cooled to room temperature, slowly poured into an ice-cooled solution of 5N sodium hydroxide (160 mL) and filtered. The filtrate was cooled in an ice-bath and acidified to pH 4 with concentrated hydrochloric acid. The precipitate was filtered, washed with water, and dried under high vacuum. The solid was re-suspended in anhydrous dichloromethane (20 mL)

and treated with a 2M solution of oxalyl chloride in dichloromethane (3.6 mL), followed by anhydrous DMF (0.1 mL). The mixture was stirred at room temperature for 1 h, filtered, and the filtrate concentrated under reduced pressure. The residue was cooled in an ice-bath and slowly treated with 28% ammonium hydroxide solution. The suspension was removed from the ice-bath, stirred at room temperature for 1 h, and filtered. The solid was washed with water and dried under high vacuum to produce 1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxamide as an off-white solid. A suspension of this carboxamide (0.13 g) in anhydrous dichloromethane (5 mL) was treated with a 2M solution of oxalyl chloride also in dichloromethane (0.5 mL) and the mixture heated at gentle reflux for 15 h. The solvent was removed under reduced pressure and the residue dissolved in anhydrous THF (1.2 mL). An aliquot of this solution (0.4 mL) was added to an ice-cooled solution of 3,4-dichloroaniline (36 mg) in anhydrous THF (0.7 mL). The ice-bath was removed and the mixture stirred at room temperature for 1 h. The precipitated solid was collected by filtration, washed with dichloromethane and MeOH, and dried under high vacuum to give the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.56 (s, 3H), 4.02 (s, 3H), 7.56-7.63 (m, 2H), 8.03 (d, J=2.2 Hz, 1H), 8.99 (d, J=2.0 Hz, 1H), 9.08 (d, J=2.0 Hz, 1H), 10.92 (s, 1H), 11.28 (s, 1H). MS (ESI) *m/z* 376, 378, 380.

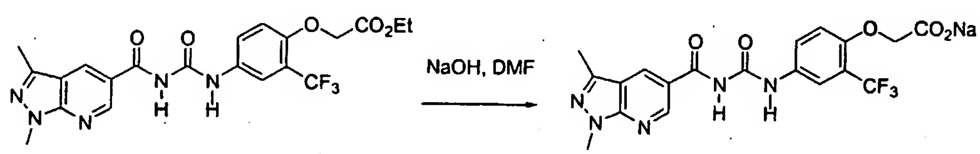
Example 3: Ethyl 2-[4-({[(1,3-dimethypyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl} amino)-2-(trifluoromethyl)phenoxy]acetate (**34**).



1,3-Dimethylpyrazolo[5,4-b]pyridine-5-carboxamide (0.35 g) was suspended in anhydrous dichloromethane (10 mL) and treated with a 2M solution of oxalyl chloride in dichloromethane (1.8 mL). The suspension was heated at gentle reflux for 15 h, cooled to room temperature, and the solvent removed under reduced pressure. The residue was dissolved in anhydrous THF

(7 mL). An aliquot of this solution (2 mL) was added to an ice-cooled solution of 4-amino-2-(trifluoromethyl)phenol (93 mg) in THF (0.5 mL). The ice-bath was removed and the reaction mixture stirred at 25°C for 1 h. The precipitated solid was collected by filtration, washed with dichloromethane and dried under high vacuum. The solid was re-suspended in acetone-DMF (8 mL:0.8 mL) and treated with potassium carbonate (0.18 g) and ethyl bromoacetate (0.15 mL). The suspension was heated at reflux for 2 h, cooled to room temperature, and concentrated under reduced pressure. The residue was treated with water (3 mL), and the resulting solids were filtered, washed with water and acetone, and dried under high vacuum to give the title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.19-1.24 (t, J=7.1 Hz, 3H), 2.58 (s, 3H), 3.99 (s, 3H), 4.14-4.21 (q, J=7.1 Hz, 2H), 4.86 (s, 2H), 7.03 (d, J=9.7 Hz, 1H), 7.52-7.60 (dd, J=2.4, 8.8 Hz, 1H), 8.09 (d, J=2.4 Hz, 1H), 8.75 (d, J=1.6 Hz, 1H), 9.22 (d, J=1.6 Hz, 1H), 12.12 (s, 1H). MS (ESI) *m/z* 480.

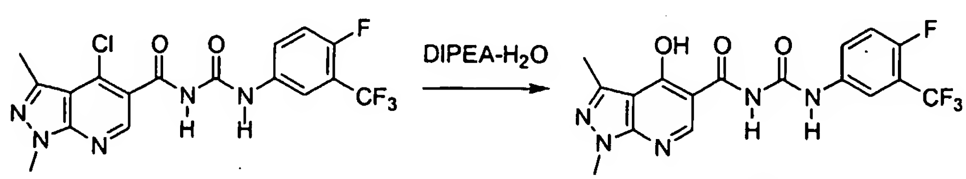
Example 4: Sodium 2-[4-({[(1,3-Dimethypyrazolo[5,4-b]pyridin-5-yl)carbonyl-amino]carbonyl}amino)-2-(trifluoromethyl)phenoxy]acetate (35).



A solution of ethyl 2-[4-({[(1,3-dimethypyrazolo[5,4-b]pyridin-5-yl)carbonyl-amino]carbonyl}amino)-2-(trifluoromethyl)phenoxy]acetate (0.11 g) in DMF (3 mL) was treated with 5N sodium hydroxide solution (1.6 mL). The mixture was stirred at room temperature for 1.25 h, and then concentrated under reduced pressure. The residue was taken up in water (4 mL), filtered, and the filtrate was cooled in an ice-bath and acidified to pH 4 with concentrated hydrochloric acid. The precipitated solid was collected by filtration, washed with water, and dried under high vacuum. A portion of this material was suspended in water (5 mL) and treated with 5N sodium hydroxide solution (27 μL). The mixture was sonicated, filtered, and the filtrate lyophilized to yield the title compound. ^{1}H NMR (DMSO-d_6) δ 2.53 (s, 3H), 3.99 (s, 3H), 4.17 (s, 2H), 6.85 (d, J=8.8 Hz,

1H), 7.44-7.47 (br d, J=8.8 Hz, 1H), 8.03 (d, J=2.1 Hz, 1H), 8.52 (s, 1H) 8.79 (d, J=1.6 Hz, 1H), 9.23 (d, J=1.6 Hz, 1H), 11.50 (br s, 1H). MS (ESI) *m/z* 450.

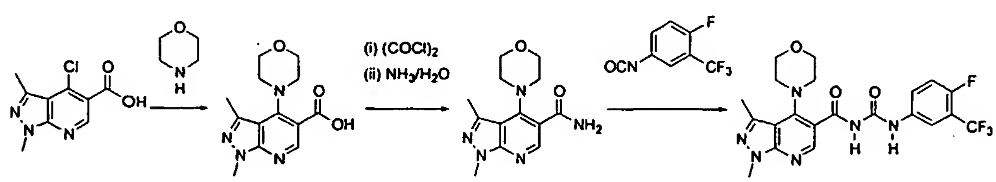
Example 5: N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(4-hydroxy-1,3- dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**43**).



43

A suspension of (4-chloro-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (0.050 g) in THF (5 mL) was dissolved in a 1:3 mixture of *N,N*-diisopropylethylamine (DIPEA) and water (4 mL). The solution was stirred at room temperature for 24 h, concentrated, and the residue purified by column chromatography on silica-gel eluting with 3:1 EtOAc-MeOH to give the title compound as a white powder. ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H), 3.75 (s, 3H), 7.45 (dd, J=9.9, 9.9 Hz, 1H), 7.81 (m, 1H), 8.11 (dd, J=6.6, 2.6 Hz, 1H), 8.58 (s, 1H), 11.51 (br s, 1H). MS (ESI) *m/z* 410.

Example 6: (1,3-Dimethyl-4-morpholin-4-ylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro -3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**65**).

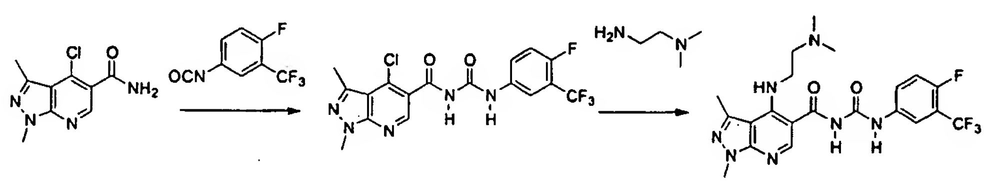


65

A solution of 4-chloro-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxylic acid (450 mg) and morpholine (870 mg) in DMF (15 mL) was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The residue was treated with water (10 mL), and the resulting solid was filtered,

washed with water, and dried under high vacuum. The solid was suspended in anhydrous dichloromethane (20 mL) and treated with oxalyl chloride (1.0 mL) and anhydrous DMF (0.1 mL). The mixture was stirred at room temperature for 1 h, filtered, and the filtrate was concentrated under reduced pressure. The residue was cooled in an ice-bath and slowly treated with a saturated solution of ammonia in THF (20 mL). The suspension was removed from the ice-bath, stirred at room temperature for 1 h, and filtered. The solid was washed with water and dried under high vacuum to give 1,3-dimethyl-4-morpholin-4-ylpyrazolo[5,4-b]pyridine-5-carboxamide as a white powder. A portion of this material (0.33 g) was dissolved in hot toluene (30 mL) and azeotroped for 1 h. The solution was cooled to room temperature and treated with 4-fluoro-3-(trifluoromethyl)phenylisocyanate (0.27 g). The mixture was refluxed for 16 h and then cooled to room temperature. The precipitated solid was filtered, washed with toluene, and dried under high vacuum to give the title compound as a white powder. ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H), 3.27 (m, 4H), 3.80 (m, 4H), 3.93 (s, 3H), 7.50 (dd, J=9.9, 9.9 Hz, 1H), 7.92 (m, 1H), 8.13 (dd, J=6.6, 2.6 Hz, 1H), 8.38 (s, 1H), 10.72 (s, 1H), 11.34 (s, 1H). MS (ESI) *m/z* 479.

<u>**Example 7**</u>: (4-{[2-(Dimethylamino)ethyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (<u>**45**</u>).



<u>**45**</u>

4-Chloro-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxamide (0.10 g) was dissolved in hot toluene (30 mL) and azeotroped for 1 h. The solution was cooled to room temperature and reacted with 4-fluoro-3-(trifluoromethyl)phenylisocyanate (0.10 g). The mixture was refluxed for 16 h and then cooled to room temperature. The precipitated solid was filtered, washed with methanol, and dried under high vacuum to give (4-chloro-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)

phenyl]amino}carbonyl)carboxamide as a white powder. A portion of this material (0.050 g) was dissolved in THF (10 mL) and reacted with (2-aminoethyl)dimethylamine (0.10 g). The mixture was stirred at room temperature for 5 h, and then concentrated under reduced pressure. The residue was treated with water (10 mL), and the resulting solid was filtered, washed with water, and dried under high vacuum. A portion of this material was suspended in water (5 mL) and treated with 1N hydrochloric acid solution (100 μL). The mixture was sonicated, filtered, and the filtrate lyophilized to give (4-{[2-(dimethylamino)ethyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride as a white powder. ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 6H), 2.53 (t, J=5.8 Hz, 2H), 2.61 (s, 3H), 3.62 (t, J=5.8 Hz, 2H), 3.86 (s, 3H), 7.50 (dd, J=10.3, 9.5 Hz, 1H), 7.76 (br s, 1H), 7.86 (m, 1H), 8.09 (dd, J=6.6, 2.6 Hz, 1H), 8.40 (s, 1H), 10.74 (s, 1H), 10.97 (br s, 1H). MS (ESI) *m/z* 480.

The following additional compounds were prepared by the foregoing procedures:

[4-(Dimethylamino)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**44**).

^{1}H NMR (DMSO-d_6) δ 2.59 (s, 3H), 3.04 (s, 6H), 3.90 (s, 3H), 7.50 (dd, J=9.9, 9.9 Hz, 1H), 7.90 (m, 1H), 8.11 (dd, J=3.6, 2.6 Hz, 1H), 8.29 (s, 1H), 10.79 (s, 1H), 11.18 (s, 1H). MS (ESI) *m/z* 437.

(4-{[2-(Dimethylamino)ethyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**46**).

^{1}H NMR (DMSO-d_6) δ 2.69 (s, 3H), 2.79 (d, J=4.4 Hz, 6H), 3.40 (m, 2H), 3.83 (m, 2H), 3.89 (s, 3H), 7.52 (dd, J=9.9, 9.9 Hz, 1H), 7.65 (br s, 1H), 7.88 (m, 1H), 8.08 (dd, J=6.6, 2.6 Hz, 1H), 8.47 (s, 1H), 10.67 (br s, 1H), 10.73 (s, 1H), 11.13 (s, 1H).

(4-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**47**).

^{1}H NMR (DMSO-d_6) δ 2.01 (s, 6H), 2.53 (t, J=5.8 Hz, 2H), 2.59 (s, 3H), 3.04 (s, 3H), 3.63 (t, J=5.8 Hz, 2H), 3.92 (s, 3H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.90 (m, 1H), 8.14 (dd, J=3.6, 2.6 Hz, 1H), 8.38 (s, 1H), 10.99 (s, 1H), 11.99 (s, 1H). MS (ESI) *m/z* 494.

(4-{[3-(Dimethylamino)propyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**49**).
^{1}H NMR (DMSO-d_6) δ 1.77 (m, 2H), 2.14 (s, 6H), 2.36 (t, J=6.6 Hz, 2H), 2.59 (s, 3H), 3.45 (t, J=6.6 Hz, 2H), 3.86 (s, 3H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.85 (m, 1H), 8.08 (m, 1H), 8.41 (s, 1H), 10.78 (br s, 1H). MS (ESI) *m/z* 494.

{4-[Bis(2-hydroxyethyl)amino]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**51**).
^{1}H NMR (DMSO-d_6) δ 2.59 (s, 3H), 3.52 (m, 4H), 3.62 (m, 4H), 3.92 (s, 3H), 5.12 (br s, 2H), 7.53 (dd, J=9.9, 8.9 Hz, 1H), 7.90 (m, 1H), 8.20 (dd, J=6.6, 2.6 Hz, 1H), 8.36 (s, 1H), 10.86 (s, 1H), 11.31 (br s, 1H). MS (ESI) *m/z* 497.

{1,3-Dimethyl-4-[methyl(1-methylpyrrolidin-3-yl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**53**).
^{1}H NMR (DMSO-d_6) δ 1.97 (m, 2H), 2.22 (s, 3H), 2.28 (m, 1H), 2.54 (m, 1H), 2.58 (s, 3H), 2.60-2.80 (m, 2H), 2.90 (s, 3H), 3.93 (s, 3H), 4.24 (m, 1H), 7.50 (dd, J=10.3, 9.5 Hz, 1H), 7.90 (m, 1H), 8.12 (dd, J=6.6, 2.6 Hz, 1H), 8.41 (s, 1H), 10.7 (br s, 1H), 11.4 (br s, 1H). MS (ESI) *m/z* 506.

{4-[(4-Aminocyclohexyl)amino]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**55**).
^{1}H NMR (DMSO-d_6) δ 1.64-1.83 (m, 8H), 2.63 (s, 3H), 3.18 (m, 1H), 3.88 (s, 3H), 4.08 (m, 1H), 7.52 (m, 1H), 7.88 (m, 1H), 8.10 (m, 1H), 8.57 (s, 1H), 10.6 (br s, 1H), 10.9 (br s, 1H). MS (ESI) *m/z* 506.

{1,3-Dimethyl-4-[(perhydropyrrolizin-7a-ylmethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**57**).
^{1}H NMR (DMSO-d_6) δ 1.59-1.81 (m, 8H), 2.59 (s, 3H) , 2.85-3.03 (m, 2H), 2.93 (d, J=6.2 Hz, 2H), 3.85 (s, 3H), 7.48 (dd, J=9.9, 9.5 Hz, 1H), 7.59 (br s, 1H), 7.82

(m, 1H), 8.10 (dd, J=6.2, 2.6 Hz, 1H), 8.50 (s, 1H), 10.9 (br s, 1H). MS (ESI) *m/z* 532.

{1,3-Dimethyl-4-[(2-perhydropyrrolizin-7a-ylethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**59**).
^{1}H NMR (DMSO-d_6) δ 1.57-1.78 (m, 10H), 2.57 (m, 2H), 2.60 (s, 3H) , 2.90 (m, 2H), 3.33 (t, J=6.2 Hz, 2H), 3.84 (s, 3H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.87 (m, 1H), 8.12 (dd, J=6.2, 2.6 Hz, 1H), 8.28 (s, 1H), 10.82 (br s, 1H), 11.52 (s, 1H). MS (ESI) *m/z* 546.

{1,3-Dimethyl-4-[(2-perhydropyrrolizin-7a-ylethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**60**).
^{1}H NMR (DMSO-d_6) δ 1.89-2.18 (m, 10H), 2.65 (s, 3H) , 3.08 (m, 2H), 3.59 (m, 2H), 3.90 (s, 3H), 7.51 (dd, J=9.9, 9.5 Hz, 1H), 7.87 (m, 1H), 8.01 (br s, 1H), 8.07 (dd, J=6.6, 2.6 Hz, 1H), 8.50 (s, 1H), 10.58 (br s, 1H), 11.71 (s, 1H), 11.11 (s, 1H).

(1,3-Dimethyl-4-piperidylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**64**).
^{1}H NMR (DMSO-d_6) δ 1.62 (m, 2H), 1.71 (m, 4H), 2.62 (s, 3H), 3.24 (m, 4H), 3.92 (s, 3H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.92 (m, 1H), 8.12 (dd, J=6.2, 2.6 Hz, 1H), 8.35 (s, 1H), 10.71 (s, 1H), 11.31 (s, 1H). MS (ESI) *m/z* 477.

(1,3-Dimethyl-4-piperazinylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**66**).
^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H), 2.93 (m, 4H), 3.23 (m, 4H), 3.92 (s, 3H), 7.51 (dd, J=9.5, 9.5 Hz, 1H), 7.90 (m, 1H), 8.12 (dd, J=6.2, 2.6 Hz, 1H), 8.36 (s, 1H), 10.7 (br s, 1H), 11.3 (br s, 1H). MS (ESI) *m/z* 478.

[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**84**).
^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H), 2.55 (m, 4H), 2.62 (s, 3H), 3.29 (m, 4H), 3.93 (s, 3H), 7.51 (dd, J=9.9, 9.9 Hz, 1H), 7.91 (m, 1H), 8.12 (dd, J=6.2, 2.6 Hz, 1H), 8.37 (s, 1H), 10.71 (s, 1H), 11.32 (s, 1H). MS (ESI) *m/z* 492.

[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**85**).

^{1}H NMR (DMSO-d_6) δ 2.65 (s, 3H), 2.86 (d, J=4.4 Hz, 3H), 3.31 (m, 2H), 3.51 (m, 6H), 3.95 (s, 3H), 7.52 (dd, J=9.9, 9.9 Hz, 1H), 7.88 (m, 1H), 8.11 (m, 1H), 8.44 (s, 1H), 10.48 (br s, 1H), 10.74 (s, 1H), 11.38 (s, 1H).

[4-(4-Ethylpiperazinyl)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**99**).

^{1}H NMR (DMSO-d_6) δ 1.03 (t, J=6.9 Hz, 3H), 2.41 (q, J=6.9 Hz, 2H), 2.57 (m, 4H), 2.62 (s, 3H), 3.31 (m, 4H), 3.93 (s, 3H), 7.50 (dd, J=9.9, 9.9 Hz, 1H), 7.91 (m, 1H), 8.13 (dd, J=6.2, 2.6 Hz, 1H), 8.35 (s, 1H), 10.72 (s, 1H), 11.31 (s, 1H). MS (ESI) *m/z* 506.

[4-(4-Ethylpiperazinyl)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**100**).

^{1}H NMR (DMSO-d_6) δ 1.28 (d, J=7.3 Hz, 3H), 2.65 (s, 3H), 3.17-3.35 (m, 4H), 3.45-3.61 (m, 6H), 3.95 (s, 3H), 7.52 (dd, J=9.9, 9.5 Hz, 1H), 7.89 (m, 1H), 8.11 (dd, J=6.2, 2.6 Hz, 1H), 8.44 (s, 1H), 10.29 (br s, 1H), 10.74 (s, 1H), 11.39 (s, 1H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl){4-[4-(2-hydroxyethyl)piperazinyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}carboxamide (**101**).

^{1}H NMR (DMSO-d_6) δ 2.47 (t, J=5.9Hz, 2H), 2.62 (s, 3H), 2.63 (m, 4H), 3.28 (m, 4H), 3.53 (m, 2H), 3.92 (s, 3H), 4.38 (br s, 1H), 7.51 (dd, J=9.9, 9.5 Hz, 1H), 7.92 (m, 1H), 8.13 (dd, J=6.2, 2.6 Hz, 1H), 8.35 (s, 1H), 10.7 (br s, 1H), 11.3 (br s, 1H). MS (ESI) *m/z* 522.

[1,3-Dimethyl-4-(4-phenylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**103**).

^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H), 3.36 (m, 4H), 3.43 (m, 4H), 3.94 (s, 3H), 6.81 (t, J=7.3 Hz, 1H), 7.01 (d, J=8.1 Hz, 1H), 7.23 (dd, J=8.1, 7.3 Hz, 1H), 7.49 (dd, J=9.9, 9.5 Hz, 1H), 7.91 (m, 1H), 8.12 (dd, J=6.3, 2.6 Hz, 1H), 8.40 (s, 1H), 10.72 (s, 1H), 11.38 (br s, 1H). MS (ESI) *m/z* 554.

{1,3-Dimethyl-4-[4-benzylpiperazinyl]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**104**).

^{1}H NMR (DMSO-d_6) δ 2.59 (m, 3H), 2.61 (s, 4H), 3.29 (m, 4H), 3.55 (s, 2H), 3.92 (s, 3H), 7.24-7.33 (m, 5H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.92 (m, 1H), 8.13 (dd, J=6.2, 2.6 Hz, 1H), 8.35 (s, 1H), 10.69 (s, 1H), 11.29 (s, 1H). MS (ESI) *m/z* 568.

4-Amino-1-{5-[N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carbamoyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-4-yl}pyridinium chloride (**106**).

^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H), 4.10 (s, 3H), 7.04 (d, J=7.3 Hz, 2H), 7.48 (dd, J=9.9, 9.5 Hz, 1H), 7.82 (m, 1H), 8.01 (dd, J=6.6, 2.6 Hz, 1H), 8.36 (d, J=7.3 Hz, 2H), 8.80 (br s, 2H), 9.06 (s, 1H), 10.4 (br s, 1H), 11.4 (br s, 1H). MS (ESI) *m/z* 486.

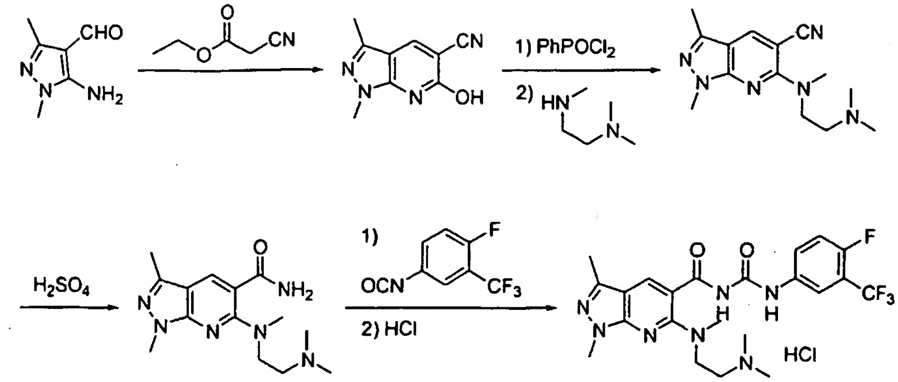
[1,3-Dimethyl-4-(4-methyl(1,4-diazaperhydroepinyl))pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**107**).

^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2H), 2.30 (s, 3H), 2.63 (s, 3H), 2.70 (m, 4H), 3.54 (m, 4H), 3.91 (s, 3H), 7.50 (dd, J=9.9, 9.5 Hz, 1H), 7.91 (m, 1H), 8.12 (m, 1H), 8.36 (s, 1H), 10.75 (s, 1H), 11.22 (s, 1H). MS (ESI) *m/z* 506.

[1,3-Dimethyl-4-(4-methyl(1,4-diazaperhydroepinyl))pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**108**).

^{1}H NMR (DMSO-d_6) δ 2.15-2.32 (m, 2H), 2.65 (s, 3H), 2.83 (d, J=4.8Hz, 3H), 3.22-3.30(m, 1H), 3.52-3.69 (m, 3H), 3.91-3.97 (m, 1H), 3.94 (s, 3H), 7.52 (dd, J=9.9, 9.5 Hz, 1H), 7.92 (m, 1H), 8.13 (dd, J=6.2, 2.6 Hz, 1H), 8.45 (s, 1H), 10.74 (br s, 1H), 10.76 (s, 1H), 11.30 (s, 1H).

Example 8: (6-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl) phenyl]amino}carbonyl)carboxamide hydrochloride (**116**).

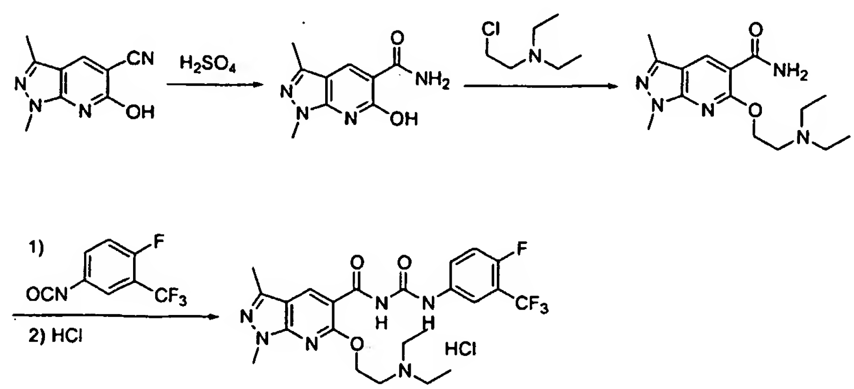


A solution of 5-amino-1,3-dimethylpyrazole-4-carbaldehyde (6.15 g) in ethyl cyanoacetate (10 mL) was stirred at 185 °C for 3 hrs. The reaction mixture was allowed to cool to room temperature. The precipitated solid was filtered, washed with ethyl acetate, and dried under high vacuum to give 6-hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-carbonitrile as a white powder.

A portion of this material (2.18 g) was dissolved in phenylphosphonic dichloride (10 mL) and stirred at 150 °C for 17 hrs. The solution was cooled to room temperature and poured into water, extracted with ethyl acetate, washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure produced a white solid. This material (2.16 g) was dissolved in tetrahydrofuran (50 mL), dimethylaminoethylmethylamine (10.6 mL) was added at room temperature, and the mixture was heated at reflux for 20 hrs. The reaction mixture was cooled to room temperature, extracted with ethyl acetate. The extract was dried over Na_2SO_4, and evaporated under reduced pressure to give 6-{[2-(dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carbonitrile as a brown oil. This material (2.96 g) was dissolved in concentrated H_2SO_4 (10 mL). The mixture was stirred at 60 °C for 15 hrs. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with dichloromethane. The extract was washed with NaCl solution, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by the recrystallization from the mixture of ethyl acetate and hexane to give 6-{[2-(dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxamide as a white solid. A portion of this

material (0.150 g) was dissolved in hot toluene (20 mL) and azeotroped for 2 hrs. The solution was cooled to room temperature and reacted with 4-fluoro-3-(trifluoromethyl)phenylisocyanate (0.180 g). The mixture was refluxed for 2 days and then cooled to room temperature. The solvent was evaporated under reduced pressure. The residue was purified with the column chromatography (ethyl acetate) to give the acylurea as a white solid. A portion of this material (52mg) was dissolved in tetrahydrofuran (1.0 mL) and treated with 1N hydrochloric acid solution (1.0 mL). This mixture was lyophilized to give (6-{[2-(dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 6H), 2.41 (s, 3H), 2.53 (t, J=6.4 Hz, 2H), 2.98 (s, 3H), 3.64 (t, J=6.4 Hz, 2H), 3.82 (s, 3H), 7.49 (m, 1H), 7.87 (m, 1H), 8.10 (m, 1H), 8.26 (s, 1H), 10.82 (br s, 1H).

<u>Example 9</u>: {6-[2-(Diethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**<u>120</u>**).



6-Hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carbonitrile (0.911 g) was dissolved in concentrated H_2SO_4 (3.0 mL) and stirred at 40 °C for 24 hrs. The solution was poured into ice-water and the precipitated solid was filtered, washed with water, and dried under high vacuum to give 6-hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-carboxamide as a white solid. A portion of this material (0.122 g) was dissolved in DMF (2.0 mL). 2-Chlorotriethylamine

hydrochloride (0.192 g) and potassium carbonate (0.304 g) were added to the solution. The reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was poured into water, extracted with ethyl acetate. The extract was washed with saturated $NaHCO_3$ solution and the brine, and dried over Na_2SO_4. The extract was evaporated under reduced pressure to give 6-[2-(diethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridine-5-carboxamide as a white solid. A portion of this material (0.059 g) was dissolved in hot toluene (10 mL) and azeotroped for 2 hrs. The solution was cooled to room temperature. 4-Fluoro-3-(trifluoromethyl) phenylisocyanate (0.098 g) was added to the solution. The mixture was heated at reflux for 23 hrs, and then, cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified with the column chromatography (ethyl acetate). A portion of this material (20mg) was dissolved in tetrahydrofuran (1.0 mL) and treated with 1N hydrochloric acid solution (1.0 mL). The mixture was lyophilized to give {6-[2-(diethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.25 (m, 8H), 2.49 (s, 3H), 3.61 (m, 2H), 3.93 (s, 3H), 4.85 (m, 2H), 7.51 (m, 1H), 7.86 (m, 1H), 8.08 (m, 1H), 8.52 (s, 1H), 10.24 (br s, 1H), 10.80 (d, J=4.0 Hz, 2H). MS (ESI) *m/z* 511 (M+H), 509 (M-H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(6-hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**109**).
^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 3.69 (s, 3H), 7.69 (t, J=10.0 Hz, 1H), 7.81 (m, 1H), 8.10 (m, 1H), 8.50 (s, 1H), 11.27 (s, 1H), 14.60 (br s, 1H). MS (ESI) *m/z* 412 (M+H), 410 (M-H).

[1,3-Dimethyl-6-(1-methylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**110**).
^{1}H NMR (DMSO-d_6) δ 1.45 (d, J=6.0 Hz, 6H), 2.48 (s, 3H), 3.90 (s, 3H), 5.53 (m, 1H), 7.50 (t, J=9.6 Hz, 1H), 7.87 (m, 1H), 8.11 (m, 1H), 8.62 (s, 1H), 10.48 (br s, 1H), 10.75 (br s, 1H). MS (ESI) *m/z* 454 (M+H), 452 (M-H).

[1,3-Dimethyl-6-(phenylmethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**111**).

^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 3.93 (s, 3H), 5.60 (s, 2H), 7.31-7.41 (m, 3H), 7.49 (t, J=9.6 Hz, 1H), 7.58 (d, J=6.8 Hz, 2H), 7.85 (m, 1H), 8.07 (m, 1H), 8.58 (s, 1H), 10.63 (br s, 1H), 10.71(br s, 1H). MS (ESI) *m/z* 502 (M+H), 500 (M-H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(6-methoxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**112**).

^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3H), 3.91 (s, 3H), 4.10(s, 3H), 7.50 (t, J=9.6 Hz, 1H), 7.88 (m, 1H), 8.09 (m, 1H), 8.55 (s, 1H), 10.62 (br s, 1H), 10.75 (br s, 1H). MS (ESI) *m/z* 426 (M+H), 424 (M-H).

(1,3-Dimethyl-6-morpholin-4-ylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**113**).

^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H), 3.34 (m, 4H), 3.75 (m, 4H), 3.87 (s, 3H), 7.50 (t, J=9.6 Hz, 1H), 7.87 (m, 1H), 8.10 (m, 1H), 8.39 (s, 1H), 10.69 (br s, 1H), 11.14 (br s, 1H). MS (ESI) *m/z* 481 (M+H), 479 (M-H).

[6-(Dimethylamino)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**114**).

^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 3.03 (s, 6H), 3.82 (m, 4H), 2.98 (s, 3H), 3.64 (t, J=6.4 Hz, 2H), 3.82 (s, 3H), 7.49 (t, J=9.6 Hz, 1H), 7.87 (m, 1H), 8.10 (m, 1H), 8.22 (s, 1H), 10.76 (br s, 1H), 11.05 (br s, 1H). MS (ESI) *m/z* 439 (M+H), 437 (M-H).

[1,3-Dimethyl-6-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**115**).

^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H), 2.80 (m, 3H), 3.12 (m, 2H), 3.48 (t, J=11.2 Hz, 1H), 3.89 (s, 3H), 7.51 (t, J=9.6 Hz, 1H), 7.87 (m, 1H), 8.09 (m, 1H), 8.41 (s, 1H), 10.74 (br s, 1H), 11.00 (br s, 1H).

{6-[2-(Dimethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**117**).

^{1}H NMR (DMSO-d_6) δ 2.49 (s, 3H), 2.88 (s, 6H), 3.60 (m, 2H), 3.93 (s, 3H), 4.86 (m, 2H), 7.51 (t, J=9.6 Hz, 1H), 7.87 (m, 1H), 8.10 (m, 1H), 8.55 (s, 1H), 10.42

(br s, 1H), 10.70 (br s, 1H), 10.78 (br s, 1H). MS (ESI) *m/z* 483 (M+H), 481 (M-H).

{6-[2-(Dimethylamino)-isopropoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**118**).

^{1}H NMR (DMSO-d_6) δ 1.44 (d, J=6.4 Hz, 3H), 2.49 (s, 3H), 2.90 (s, 6H), 3.48-3.59 (m, 2H), 3.93 (s, 3H), 5.84 (m, 2H), 7.51 (t, J=9.6 Hz, 1H), 7.86 (m, 1H), 8.10 (m, 1H), 8.55 (s, 1H), 10.02 (br s, 1H), 10.65 (s, 1H), 10.73 (s, 1H). MS (ESI) *m/z* 497 (M+H), 495 (M-H).

{6-[3-(Dimethylamino)propoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**119**).

^{1}H NMR (DMSO-d_6) δ 2.24 (m, 2H), 2.49 (s, 3H), 2.73 (s, 1H), 2.78 (s, 5H), 3.48-3.59 (m, 2H), 3.92 (s, 3H), 4.58 (t, J=5.0 Hz, 2H), 7.51 (t, J=9.6 Hz, 1H), 7.89 (m, 1H), 8.10 (m, 1H), 8.55 (s, 1H), 10.11 (br s, 1H), 10.62 (s, 1H), 10.79 (s, 1H). MS (ESI) *m/z* 497 (M+H), 495 (M-H).

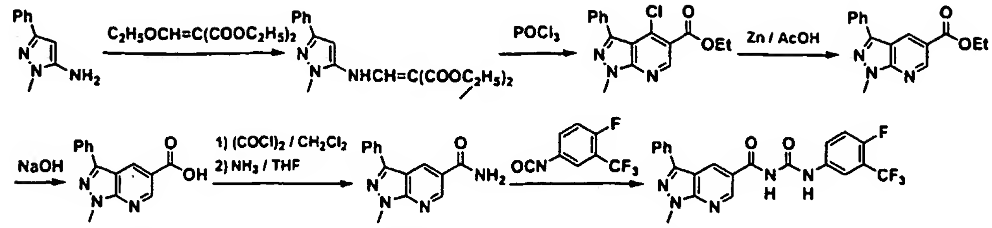
[1,3-Dimethyl-6-(2-pyrrolidinylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**121**).

^{1}H NMR (DMSO-d_6) δ 1.88-2.05 (m, 4H), 2.49 (s, 3H), 3.12-3.18 (m, 2H), 3.68 (m, 4H), 3.93 (s, 3H), 4.85 (t, J=4.8 Hz, 2H), 7.51 (t, J=9.6 Hz, 1H), 7.86 (m, 1H), 8.09 (m, 1H), 8.53 (s, 1H), 10.63 (br s, 1H), 10.62 (d, J=3.6 Hz, 2H). MS (ESI) *m/z* 509 (M+H), 507 (M-H).

[1,3-Dimethyl-6-(2-piperidylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**122**).

^{1}H NMR (DMSO-d_6) δ 1.38 (br s, 1H), 1.67-1.78 (m, 5H), 2.49 (s, 3H), 3.04 (br s, 2H), 3.57 (br s, 4H), 3.93 (s, 3H), 4.87 (br s, 2H), 7.53 (t, J=9.6 Hz, 1H), 7.88 (m, 1H), 8.09 (m, 1H), 8.54 (s, 1H), 10.17 (br s, 1H), 10.78 (s, 1H), 10.82 (s, 1H). MS (ESI) *m/z* 523 (M+H), 521 (M-H).

Example 10: N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(1-methyl-3-phenylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**123**).



A mixture of 1-methyl-3-phenylpyrazol-5-ylamine (3.46 g) and diethyl 2-(ethoxymethylene)propan-1,3-dioate (4.33 g) was heated at 120 °C for 3 hrs with stirring, and then ethanol formed in the reaction was evaporated under reduce pressure. The residue was treated with hexane (50 mL), and the precipitated solid was filtered, washed with hexane, and dried under high vacuum. The solid was dissolved in phosphorus oxychloride (20 mL), heated at reflux for 14 hrs, and the reaction mixture was concentrated under reduced pressure. The residue was treated with water (50 mL), and the resulting solid was filtered, washed with water, and dried under high vacuum to give ethyl 1-methyl-3-phenyl-4-chloro-pyrazolo[5,4-b]pyridin-5-carboxylate.

The solid was dissolved in acetic acid (20 mL), and reacted with zinc (2.00g) at 80 °C for 60 min. Zinc was removed by the filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (30 mL), and treated with 5N sodium hydroxide solution (30 mL). The mixture was heated at reflux for 6 hrs, and then solvent was evaporated under reduced pressure. The residue was poured into water (40 mL), filtered, and the filtrate was cooled in an ice-bath and acidified to pH 4 with concentrated hydrochloric acid. The precipitated solid was collected by the filtration, washed with water, and dried under high vacuum to give 1-methyl-3-phenylpyrazolo[5,4-b]pyridine-5-carboxylic acid as a white powder. The acid was suspended in anhydrous dichloromethane (50 mL) under an argon atmosphere and added oxalyl chloride (5.0 mL), followed by anhydrous DMF (0.5 mL). The mixture was stirred at room temperature for 6 hrs, and then concentrated under reduced pressure. The residue was cooled to ice-bath temperature and a saturated solution of ammonia in tetrahydrofuran (50 mL) was slowly added to the residue. The ice-bath was removed, the reaction mixture was stirred at room temperature for 6 hrs, and the precipitated solid was filtered. The solid was washed with

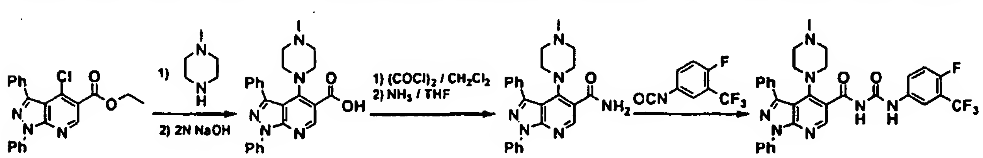
water and dried under high vacuum to give 1-methyl-3-phenylpyrazolo[5,4-b]pyridine-5-carboxamide as a white powder.

A portion of this material (50 mg) was dissolved in hot toluene (5.0 mL) and azeotroped for 6 hrs. The solution was cooled to room temperature, 4-fluoro-3-(trifluoromethyl)phenylisocyanate (45 mg) was added, and refluxed for 16 hrs. The reaction mixture was cooled to room temperature and the precipitated solid was collected by the filtration, washed with methanol, and dried under high vacuum to give N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(1-methyl-3-phenylpyrazolo[5,4-b]pyridin-5-yl)carboxamide as a white powder (45mg). ^{1}H NMR (DMSO-d_6) δ 4.17 (s, 3H), 7.49-7.62 (m, 4H), 7.93 (m, 1H), 8.12-8.15 (m, 3H), 9.15 (d, J=2.2 Hz, 1H), 9.27 (d, J=2.2 Hz, 1H), 10.98 (s, 1H), 11.49 (s, 1H). MS (ESI) *m/z* 456 (M-H), 458 (M+H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(1-methylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**124**).
^{1}H NMR (DMSO-d_6) δ 4.11 (s, 3H), 7.51 (dd, J=9.9, 9.9 Hz, 1H), 7.91 (m, 1H), 8.12 (dd, J=6.6, 2.6 Hz, 1H), 8.37 (s, 1H), 8.93 (d, J=2.2 Hz, 1H), 9.12 (d, J=2.2 Hz, 1H), 10.90 (s, 1H), 11.30 (s, 1H). MS (ESI) *m/z* 380 (M-H), 382 (M+H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(3-methyl-1-phenylpyrazolo[5,4-b]pyridin-5-yl)carboxamide (**125**).
^{1}H NMR (DMSO-d_6) δ 2.68 (s, 3H), 7.37 (m, 1H), 7.50-7.60 (m, 3H), 7.92 (m, 1H), 8.13 (dd, J=6.6, 2.6 Hz, 1H), 8.25 (dd, J=8.8, 1.1 Hz, 2H), 9.11 (d, J=2.2 Hz, 1H), 9.19 (d, J=2.2 Hz, 1H), 10.91 (s, 1H), 11.32 (s, 1H). MS (ESI) *m/z* 456 (M-H), 458 (M+H).

Example 11: N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[4-(4-methylpiperazin yl)-1,3-diphenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide (**126**).



Ethyl 4-chloro-1,3-diphenylpyrazolo[5,4-b]pyridine-5-carboxylate (900 mg) and methylpiperazine (4.50 g) were dissolved in tetrahydrofuran (90 mL) and

stirred at room temperature for 6 hrs. The reagents were removed under reduced pressure, the residue was dissolved in the mixture of ethanol (27 mL) and 5N sodium hydroxide solution (27 mL), and heated at reflux for 6 hrs. The solvent was evaporated under reduced pressure, the residue was dissolved in water (36 mL), insoluble solids were removed by the filtration. The filtrate was cooled in an ice-bath and acidified to pH 4 with concentrated hydrochloric acid. The precipitated solid was collected by the filtration, washed with water, and dried under high vacuum.

The solid was suspended in anhydrous dichloromethane (50 mL) under an argon atmosphere. Oxalyl chloride (5.0 mL) and anhydrous DMF (0.5 mL) was added to the suspension, and the reaction mixture was stirred at room temperature for 6 hrs. The oxalyl chloride was evaporated under reduced pressure, the residue was cooled in an ice bath, and a saturated solution of ammonia in tetrahydrofuran (50 mL) was slowly added. The ice bath was removed, the suspension was stirred at room temperature for 6 hrs. The precipitated solid was collected by the filtration, washed with water, and dried under high vacuum to give 1,3-diphenylpyrazolo[5,4-b]pyridine-5-carboxamide as a white powder.

A portion of this material (82 mg) was dissolved in hot toluene (8.0 mL) and azeotroped for 6 hrs. The solution was cooled to room temperature, added 4-fluoro-3-(trifluoromethyl)phenylisocyanate (49 mg), and heated at reflux for 16 hrs. The reaction mixture was cooled to room temperature, the precipitated solid was filtered, washed with methanol, and dried under high vacuum to give N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[4-(4-methylpiperazinyl)-1,3-diphenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide as a white powder.
^{1}H NMR (DMSO-d_6) δ 1.91 (m, 4H), 2.01 (s, 3H), 3.10 (m, 4H), 7.37 (m, 1H), 7.48-7.60 (m, 6H), 7.68 (m, 2H), 7.91 (m, 1H), 8.12 (m, 1H), 8.18 (dd, J=8.8, 1.1 Hz, 2H), 8.50 (s, 1H), 10.65 (s, 1H), 11.38 (s, 1H). MS (ESI) *m/z* 616 (M-H), 618 (M+H).

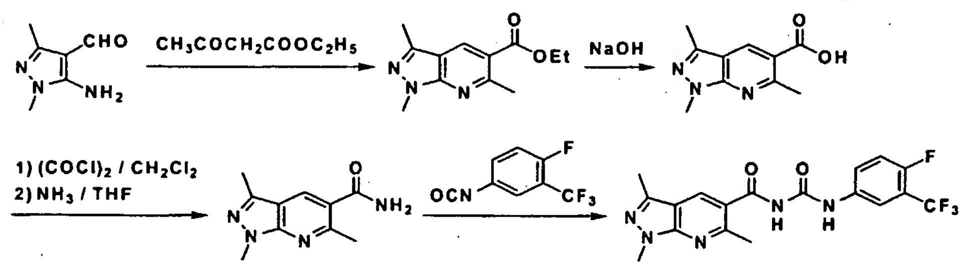
N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[4-(4-methylpiperazinyl)-1,3-diphenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride (**127**)

MS (ESI) *m/z* 616 (M-H), 618 (M+H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[1-methyl-4-(4-methylpiperazinyl)-3-phenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide (**128**)
^{1}H NMR (DMSO-d_6) δ 1.92 (m, 4H), 2.00 (s, 3H), 3.06 (m, 4H), 4.06 (s, 3H), 7.48-7.59 (m, 6H), 7.91 (m, 1H), 8.12 (m, 1H), 8.41 (s, 1H), 10.67 (s, 1H), 11.31 (s, 1H). MS (ESI) *m/z* 554 (M-H), 556 (M+H).

N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[1-methyl-4-(4-methylpiperazinyl)-3-phenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride (**129**)
MS (ESI) *m/z* 554 (M-H), 556 (M+H).

Example 12: N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl) (1,3,6-trimethylpyrazo lo[5,4-b]pyridin-5-yl)carboxamide (**130**).



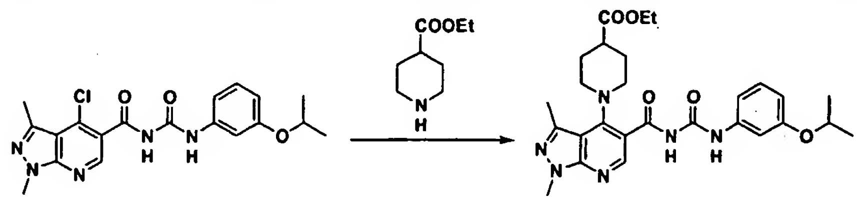
A solution of 5-amino-1,3-dimethylpyrazol-4-carbaldehyde (400 mg) and ethyl 3-oxobutanoate (600 mg) in piperidine (5 mL) was reflux for 3 hrs, the reagents were evaporated under reduced pressure, and the residue was washed with ether (5.0 mL) to give ethyl 1,3,6-trimethylpyrazolo[5,4-b]pyridin-5-yl)carboxylate as a white powder.

The solid was dissolved in the mixture of ethanol (5.0 mL) and 5N sodium hydroxide solution (5.0 mL), the solution was heated at reflux for 6 hrs, and then concentrated under reduced pressure. The residue was poured into water (4 mL), insoluble solid was removed by the filtration, the filtrate was cooled in an ice bath, and acidified to pH 4 with concentrated hydrochloric acid. The precipitated solid was collected by the filtration, washed with water, and dried under high vacuum.

The solid was suspended in anhydrous dichloromethane (5 mL) under an argon atmosphere. Oxalyl chloride (0.5 mL) and anhydrous DMF (0.05 mL) were added to the suspension, and the mixture was stirred at room temperature for 6 hrs. The reaction mixture was concentrated under reduced pressure, the residue was cooled in an ice bath, and a saturated solution of ammonia in tetrahydrofuran (5 mL) was slowly added into the residue. The ice-bath was removed and the suspension was stirred at room temperature for 1 hr. The precipitated solid was filtrated, washed with water, and dried under high vacuum to give 1,3,6-trimethylpyrazolo[5,4-b]pyridin-5-carboxamide as a white powder. A portion of this material (50 mg) was dissolved in hot toluene (5.0 mL) and azeotroped for 6 hrs. The solution was cooled to room temperature, 4-fluoro-3-(trifluoromethyl)phenylisocyanate (55 mg) was added, and refluxed for 16 hrs. The reaction mixture was cooled to room temperature, the precipitated solid was filtered, washed with methanol, and dried under high vacuum to give N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(1,3,6-trimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide as a white powder.

^{1}H NMR (DMSO-d_6) δ 2.51 (s, 3H), 2.73 (s, 3H), 3.97 (s, 3H), 7.51 (dd, J=9.9, 9.9 Hz, 1H), 7.91 (m, 1H), 8.12 (dd, J=6.2, 2.6 Hz, 1H), 8.49 (s, 1H), 10.75 (s, 1H), 11.16 (s, 1H). MS (ESI) *m/z* 408 (M-H), 410 (M+H).

Example 13: Ethyl 1-{1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino} carbonyl) carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}piperidine-4-carboxylate (**131**).



(4-Chloro-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carboxamide (40 mg) was dissolved in tetrahydrofuran (5.0 mL), ethyl piperidin-4-carboxylate (160 mg) was added , and the mixture was stirred at room temperature for 5 hrs. The solvent was evaporated under reduced pressure, the residue was suspended in water (10 mL), the resulting solid was filtered, washed with water, and dried under high vacuum to give ethyl 1-{1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}piperidin-4-carboxylate as a white powder.

^{1}H NMR (DMSO-d_6) δ 1.19 (t, J=7.3 Hz, 3H), 1.27 (d, J=5.9 Hz, 6H), 1.79 (m, 2H), 1.98 (m, 2H), 2.57 (m, 1H), 2.61 (s, 3H), 3.14 (m, 2H), 3.41 (m, 2H), 3.92 (s, 3H), 4.09 (q, J=7.3 Hz, 2H), 4.59 (m, 1H), 6.67 (dd, J=8.1, 1.1 Hz, 1H), 7.05 (dd, J=8.1, 2.6 Hz, 1H), 7.25 (m, 2H), 8.36 (s, 1H), 10.54 (s, 1H), 11.18 (s, 1H). MS (ESI) *m/z* 521 (M-H), 523 (M+H).

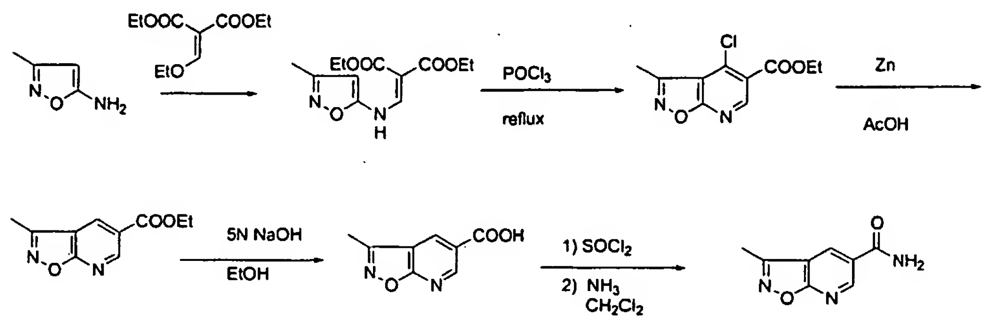
tert-Butyl 2-({1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl) carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}amino)acetate carboxamide (**132**).

^{1}H NMR (DMSO-d_6) δ 1.28 (d, J=6.2 Hz, 3H), 1.42 (s, 9H), 2.63 (s, 3H), 3.87 (s, 3H), 4.21 (d, J=5.9 Hz, 2H), 4.59 (m, 1H), 6.67 (dd, J=7.4, 1.8 Hz, 1H), 7.02 (dd, J=7.7, 2.6 Hz, 1H), 7.24 (m, 2H), 7.99 (br, 1H), 8.44 (s, 1H), 10.57 (s, 1H), 10.91 (s, 1H). MS (ESI) *m/z* 495 (M-H), 497 (M+H).

tert-Butyl 2-({1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl) carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}methylamino)acetate (**133**).

^{1}H NMR (DMSO-d$_6$) δ 1.27 (d, J=5.9 Hz, 3H), 1.42 (s, 9H), 2.64 (s, 3H), 3.06 (s, 3H), 3.88 (s, 2H), 3.93 (s, 3H), 4.60 (m, 1H), 6.67 (dd, J=8.0, 1.8 Hz, 1H), 7.06 (dd, J=8.1, 1.1 Hz, 1H), 7.25 (m, 2H), 8.41 (s, 1H), 10.57 (s, 1H), 11.02 (s, 1H). MS (ESI) *m/z* 509 (M-H), 511 (M+H).

Example 14: 3-methylisoxazolo[5,4-b]pyridine-5-carboxamide.

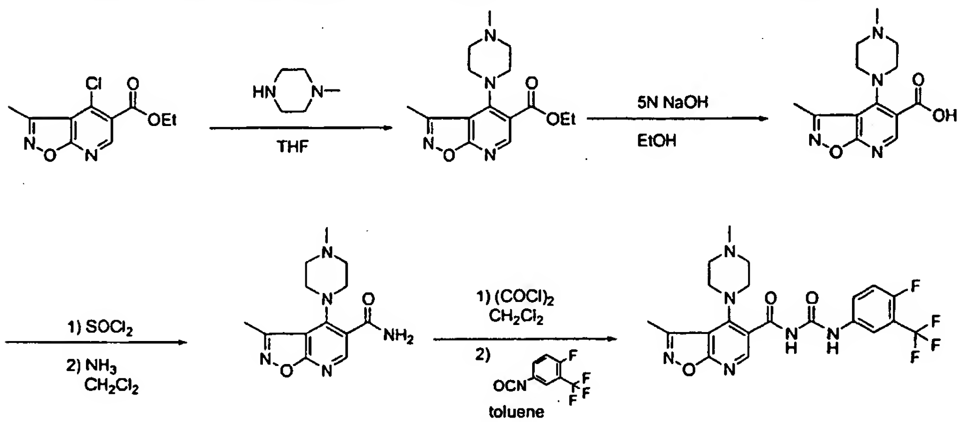


A mixture of 5-amino-3-methyl-isoxazole (5.26 g) and diethyl ethoxymethylenemalonate (10.9 ml) was heated at 120 °C for 3 hrs. The mixture was cooled to room temperature. The precipitated solid was collected, washed with n-hexane and dried under high vacuum. A portion of this solid (11.37 g) was dissolved in phosphoryl chloride (55 ml), heated at reflux for 11 hrs, and then cooled to room temperature. The mixture was concentrated under reduced pressure and the residue was purified with the column chromatography (ethyl acetate: n-hexane = 1: 9) to give ethyl 3-methylisoxazolo[5,4-b]pyridine-5-carboxylate as a white solid. Zinc powder (2.75 g) was added to a solution of a portion of the solid (2.43 g) in acetic acid (24 ml), the mixture was stirred at 80 °C for 1.5 hrs, and then filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of 5N NaOH (10 ml) and ethanol (10 ml), the solution was refluxed for 1.5 hrs, cooled to room temperature, and acidified with concentrated HCl. The precipitated solid was collected by the filtration, washed with water, and dried under high vacuum.

The solid was suspended in thionyl chloride (50 ml) and heated at 50 °C for 5 hrs. The thionyl chloride was evaporated under reduced pressure, the residue was dissolved with dichloromethane (5 ml), and reacted with ammonia gas at room temperature for 1 day. The reaction mixture was concentrated

under reduced pressure, and the residue was treated with water. The precipitated solid was filtered, washed with water, and dried under high vacuum to give 3-methylisoxazolo[5,4-b]pyridine-5-carboxamide. Such a carboxamide may be reacted with an isocyanate or an amine to produce an acylurea compound of the invention according to Procedure A or B, respectively, above. ^{1}H NMR (DMSO-d_6) δ 2.62 (s, 3H), 7.72 (br.s, 1H), 8.27 (br.s, 1H), 8.87 (d, J=2.0Hz, 1H), 9.11 (d, J=2.0Hz, 1H). MS (ESI) m/z 176 (M-H).

Example 15: N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[3-methyl-4-(4-methylpiperazinyl)isoxazolo[5,4-b]pyridin-5-yl]carboxamide (**134**).



A solution of ethyl 4-chloro-3-methylisoxazolo[5,4-b]pyridin-5-carboxylate (1.02 g) and 1-methylpiperazine (1.12 ml) in tetrahydrofuran (10 ml) was stirred at room temperature for 1 hr and then concentrated under reduced pressure. The residue was treated with water, the precipitated solid was filtered, washed with water, and dried under high vacuum. This solid was suspended in ethanol (11ml), added 5N NaOH (11 ml), and the mixture was stirred at 60 °C for 1 hr. The reaction mixture was treated with 5N HCl and purified by ODS column (VARIAN MEGABOND ELUT C18) to give 3-methyl-4-(4-methyl-piperazin-1-yl) isoxazolo[5,4-b]pyridine-5-carboxylic acid as an amorphous solid. A portion of this amorphous solid (417 mg) was dissolved in thionyl chloride (40 ml) and heated at 50 °C for 3.5 hrs. The mixture was concentrated under reduced pressure, the residue was dissolved in THF (20 ml), and reacted with ammonia gas at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, the residue was treated with water, the resulting solid was

filtered, washed with water, and dried under high vacuum to give the 3-methyl-4-(4-methyl-piperazin-1-yl)-isoxazolo[5,4-b]pyridine-5-carboxylic acid amide.

A portion of this material (50 mg) was dissolved in toluene (5 ml) and azeotroped for 3 hrs. The solution was cooled to room temperature and then reacted with 4-fluoro-3-(trifluoromethyl)phenyl isocyanate (0.031 ml). The mixture was refluxed for 3 hrs and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified with p-TLC (methanol) to give N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[3-methyl-4-(4-methylpiperazinyl)isoxazolo[5,4-b]pyridin-5-yl]carboxamide (**134**).
^{1}H NMR (DMSO-d_6) delta ppm: 2.23 (s, 3H), 2.64 (s, 3H), 3.16-3.51(m, 8H), 7.45 (t, J=9.7Hz, 1H), 7.84 (m, 1H), 8.13 (m, 1H), 8.39 (s, 1H). MS (ESI) m/z 481 (M+H), 479 (M-H).

N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)[3-methyl-4-(4-methylpiperazinyl)isoxazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride (**135**).
^{1}H NMR (DMSO-d_6) δ 2.50 (m, 3H), 2.69 (s, 3H), 3.25-3.42 (m, 8H), 7.53 (t, J=9.8Hz, 1H), 7.89 (m, 1H), 8.11 (m, 1H), 8.56 (br.s, 1H), 10.61 (br.s, 1H), 11.48 (br.s, 1H). MS (ESI) m/z 481 (M+H), 479 (M-H).

[4-(dimethylamino)-3-methylisoxazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**136**).
^{1}H NMR (DMSO-d_6) δ 2.64 (s, 3H), 3.10 (s, 6H), 7.53 (t, J=9.9Hz, 1H), 7.91 (m, 1H), 8.11 (m, 1H), 8.36 (s, 1H), 10.68 (br.s, 1H), 11.32(br.s, 1H). MS (ESI) m/z 426 (M+H), 424 (M-H).

(4-{[2-(dimethylamino)ethyl]methylamino}-3-methylisoxazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide (**137**).
^{1}H NMR (DMSO-d_6) δ 2.50 (s, 6H), 2.65 (s, 3H), 3.08 (s, 3H), 3.35 (m, 2H), 3.58 (m, 2H), 7.52 (t, J=9.7Hz, 1H), 7.91 (m, 1H), 8.14 (m, 1H), 8.46 (s, 1H),10.80 (br.s 1H). MS (ESI) m/z 483 (M+H), 481 (M-H).

(4-{[2-(dimethylamino)ethyl]methylamino}-3-methylisoxazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride (**138**).

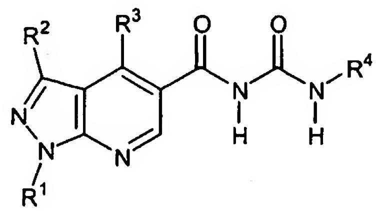
^{1}H NMR (DMSO-d_6) δ 2.69 (s, 3H), 2.75 (br.d, J=4Hz, 6H), 3.17 (br.s, 3H), 3.37 (m, 2H), 3.76 (m, 2H), 7.53 (t, J=9.5Hz, 1H), 7.88 (m, 1H), 8.10 (m, 1H), 8.52 (s, 1H),10.44 (br.s, 1H), 10.67 (br.s, 1H), 11.39 (br.s, 1H). MS (ESI) m/z 483 (M+H), 481 (M-H).

N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(3-methyl-4-morpholin-4-ylisoxazolo[5,4-b]pyridin-5-yl)carboxamide (139).

^{1}H NMR (DMSO-d_6) δ 2.66 (s, 3H), 3.79 (m, 4H), 7.52 (t, J=9.7 Hz, 1H), 7.91 (1Hrs), 8.12 (m, 1H), 8.50 (s, 1H), 10.63 (br.s, 1H), 11.48 (br.s, 1H). MS (ESI) m/z 468 (M+H), 466 (M-H).

Compounds of General Formulae III to VI:

The compounds shown in Tables 1 to 4 were prepared either by the procedures described above or by modifications of these procedures familiar to those skilled in the art.



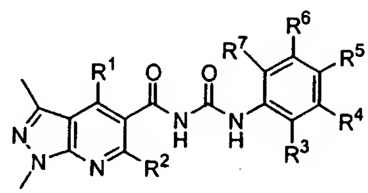
III

Table 1

Cmpd	R^1	R^2	R^3	R^4	MW	MS (m/z)
1	Me	Me	H	4-fluorophenyl	327.32	326
2	Me	Me	H	3,4-dichlorophenyl	378.22	376, 378, 380
3	Me	Me	H	3-chlorophenyl	343.77	342, 344
4	Me	Me	H	2,4-dichlorophenyl	378.22	376, 378, 380
5	Me	Me	H	4-chlorophenyl	343.77	342, 344
6	Me	Me	H	4-iodophenyl	435.22	434
7	Me	Me	H	3-cyanophenyl	334.34	333
8	Me	Me	H	3-bromophenyl	388.23	388, 390

Cmpd	R^1	R^2	R^3	R^4	MW	MS (m/z)
9	Me	Me	H	3-chloro-4-hydroxyphenyl	359.77	358, 360
10	Me	Me	H	3,5-bis(trifluoromethyl)phenyl	445.32	444
11	Me	Me	H	4-fluoro-3-(trifluoromethyl)phenyl	395.32	394
12	Me	Me	H	3-fluoro-4-(trifluoromethyl)phenyl	395.32	394
13	Me	Me	H	4-nitro-3-(trifluoromethyl)phenyl	422.32	421
14	Me	Me	H	2,3-dichlorophenyl	378.22	376, 378, 380
15	Me	Me	H	2,6-dichlorophenyl	378.22	376, 378, 380
16	Me	Me	H	2,5-dichlorophenyl	378.22	376, 378, 380
17	Me	Me	H	3,5-dichlorophenyl	378.22	376, 378, 380
18	Me	Me	H	2-chloro-5-(trifluoromethyl)phenyl	411.77	410, 412
19	Me	Me	H	4-chloro-2-(trifluoromethyl)phenyl	411.77	410, 412
20	Me	Me	H	2-chloro-4-(trifluoromethyl)phenyl	411.77	410, 412
21	Me	Me	H	4-chloro-3-(trifluoromethyl)phenyl	411.77	410, 412
22	Me	Me	H	2,5-bis(trifluoromethyl)phenyl	445.32	444
23	Me	Me	H	3,4-bis(trifluoromethyl)phenyl	445.32	444
24	Me	Me	H	3-iodophenyl	435.22	434
25	Me	Me	H	3-chloro-4-(carboxymethyleneoxy)phenyl	417.81	416
26	Me	Me	H	3-(trifluoromethyl)phenyl	377.33	376
27	Me	Me	H	4-hydroxy-3-(trifluoromethyl)phenyl	393.32	392
28	Me	Me	H	5-hydroxy-3-(trifluoromethyl)phenyl	393.32	392
29	Me	Me	H	5-carboxy-3-(trifluoromethyl)phenyl	421.33	420
30	Me	Me	H	3-isopropoxyphenyl	367.41	366
31	Me	Me	H	3-phenoxyphenyl	401.43	400
32	Me	Me	H	3-phenylphenyl	385.43	384
33	Me	Me	H	4-carboxy-3-isopropoxyphenyl	411.42	410

Cmpd	R^1	R^2	R^3	R^4	MW	MS (m/z)
34	Me	Me	H	3-trifluoromethyl-4-(ethoxycarbonylmethyleneoxy)phenyl	479.41	480
35	Me	Me	H	3-trifluoromethyl-4-(carboxymethyleneoxy)phenyl	451.36	450
36	Me	Me	Cl	3-chlorophenyl	378.22	376, 378, 380
37	Me	Me	Cl	3,4-dichlorophenyl	412.66	374, 376, 378
38	Me	Me	Cl	4-(trifluoromethyl)phenyl	411.77	374
39	Me	Me	Cl	4-chlorophenyl	378.22	340, 342
40	Me	Me	H	3-chloro-4-(carboxymethyleneoxy)phenylsodium salt	439.82	416
41	Me	Me	H	4-carboxyphenyl	353.34	352
42	Me	Me	H	3-(trifluoromethyl)phenyl	377.32	376



IV

Table 2

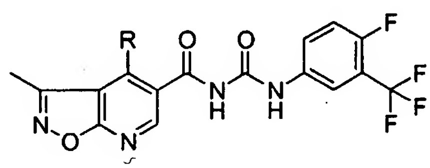
Cmpd	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Salt	MW	MS (m/z)
43	OH	H	H	CF_3	F	H	H	---	411.31	410
44	Me_2N-	H	H	CF_3	F	H	H	---	438.38	437
45	$Me_2NCH_2CH_2NH$-	H	H	CF_3	F	H	H	---	481.45	480
46	$Me_2NCH_2CH_2NH$-	H	H	CF_3	F	H	H	HCl	517.91	ND
47	$Me_2NCH_2CH_2N(Me)$-	H	H	CF_3	F	H	H	---	495.48	494
48	$Me_2NCH_2CH_2N(Me)$-	H	H	CF_3	F	H	H	HCl	531.94	ND
49	$Me_2N(CH_2)_3NH$-	H	H	CF_3	F	H	H	---	495.48	494

50	$Me_2N(CH_2)_3NH$-	H	H	CF_3	F	H	H	HCl	531.94	ND
51	$-N(CH_2CH_2OH)_2$	H	H	CF_3	F	H	H	---	498.44	497
52	2-(4-morpholinyl) ethylamino	H	H	CF_3	F	H	H	---	523.49	522
53	methyl (1-methylpyrrolidin-3-yl)amino	H	H	CF_3	F	H	H	---	507.49	506
54	methyl (1-methylpyrrolidin-3-yl)amino	H	H	CF_3	F	H	H	HCl	543.95	ND
55	(4-aminocyclohexyl) amino	H	H	CF_3	F	H	H	---	507.49	506
56	(4-aminocyclohexyl) amino	H	H	CF_3	F	H	H	HCl	543.95	ND
57	2-perhydropyrrolizin-7a-ylmethylamino	H	H	CF_3	F	H	H	---	533.53	532
58	2-perhydropyrrolizin-7a-ylmethylamino	H	H	CF_3	F	H	H	HCl	569.99	ND
59	2-perhydropyrrolizin-7a-ylethylamino	H	H	CF_3	F	H	H	---	547.56	546
60	2-perhydropyrrolizin-7a-ylethylamino	H	H	CF_3	F	H	H	HCl	584.02	ND
61	benzylamino	H	H	CF_3	F	H	H	---	500.46	499
62	3-(dimethylamino) pyrrolidinyl	H	H	CF_3	F	H	H	---	507.49	506
63	3-(dimethylamino) pyrrolidinyl	H	H	CF_3	F	H	H	HCl	543.95	ND
64	piperidyl	H	H	CF_3	F	H	H	---	478.45	477
65	4-morpholyl	H	H	CF_3	F	H	H	---	480.43	479
66	4-piperazinyl	H	H	CF_3	F	H	H	---	479.44	478
67	4-piperazinyl	H	H	CF_3	F	H	H	HCl	515.90	ND
68	4-methylpiperazinyl	H	H	Cl	H	H	H	HCl	478.38	440, 442
69	4-methylpiperazinyl	H	H	Br	H	H	H	HCl	522.84	486
70	4-methylpiperazinyl	H	H	H	Cl	H	H	---	441.92	440

71	4-methylpiperazinyl	H	H	Cl	Cl	H	H	---	476.37	474, 476
72	4-methylpiperazinyl	H	H	CF_3	H	H	H	---	475.47	474
73	4-methylpiperazinyl	H	H	CF_3	H	H	H	HCl	511.94	474
74	4-methylpiperazinyl	H	H	i-Pr	H	H	H	HCl	486.02	448
75	4-methylpiperazinyl	H	H	O-i-Pr	H	H	H	HCl	502.02	464
76	4-methylpiperazinyl	H	H	O-i-Pr	CO_2H	H	H	---	509.57	508
77	4-methylpiperazinyl	H	H	OCF_3	H	H	H	HCl	527.93	490
78	4-methylpiperazinyl	H	H	1,3-Thiazol-2-yl	H	H	H	---	490.59	489
79	4-methylpiperazinyl	H	H	1,3-Thiazol-2-yl	H	H	H	HCl	527.05	ND
80	4-methylpiperazinyl	H	H	Ph	H	H	H	---	483.58	482
81	4-methylpiperazinyl	H	H	Ph	H	H	H	HCl	520.04	482
82	4-methylpiperazinyl	H	H	OPh	H	H	H	---	499.57	498
83	4-methylpiperazinyl	H	H	CF_3	Me	H	H	HCl	525.96	488
84	4-methylpiperazinyl	H	H	CF_3	F	H	H	---	493.46	492
85	4-methylpiperazinyl	H	H	CF_3	F	H	H	HCl	529.93	ND
86	4-methylpiperazinyl	H	H	F	CF_3	H	H	---	493.46	492
87	4-methylpiperazinyl	H	H	CF_3	OH	H	H	---	491.47	490
88	4-methylpiperazinyl	H	H	CF_3	OH	H	H	HCl	527.93	ND
89	4-methylpiperazinyl	H	H	CF_3	H	OH	H	---	491.47	490
90	4-methylpiperazinyl	H	H	CF_3	H	OH	H	HCl	527.93	ND
91	4-methylpiperazinyl	H	H	CF_3	H	CF_3	H	HCl	579.93	542

92	4-methylpiperazinyl	H	H	CO_2i-Pr	Cl	H	H	HCl	564.47	526
93	4-methylpiperazinyl	H	H	PhC(=O)-	H	H	H	HCl	548.05	510
94	4-phenylpiperazinyl	H	H	Cl	4-Morpholinyl carbonyl	H	H	---	555.04	553
95	4-methylpiperazinyl	H	H	4-Morpholinyl carbonyl	Cl	H	H	HCl	592.51	555, 557
96	4-methylpiperazinyl	H	H	4-methylpiperazinyl carbonyl	Cl	H	H	---	568.08	566
97	4-methylpiperazinyl	H	H	Cl	4-methylpiperazinylcarbonyl	H	H	---	568.08	566
98	4-methylpiperazinyl	H	H	CF_3	F	H	H	Me-I	635.40	508
99	4-ethylpiperazinyl	H	H	CF_3	F	H	H	---	507.49	506
100	4-ethylpiperazinyl	H	H	CF_3	F	H	H	HCl	543.95	ND
101	4-(2-hydroxyethyl)piperazinyl	H	H	CF_3	F	H	H	---	523.49	522
102	4-(2-hydroxyethyl)piperazinyl	H	H	CF_3	F	H	H	HCl	559.95	ND
103	4-phenylpiperazinyl	H	H	CF_3	F	H	H	---	555.54	554
104	4-benzylpiperazinyl	H	H	CF_3	F	H	H	---	569.56	568
105	4-benzylpiperazinyl	H	H	CF_3	F	H	H	HCl	606.02	ND
106	4-aminopyridinyl	H	H	CF_3	F	H	H	HCl	523.88	486
107	4-methyl-1,4-diazaperhydroepinyl	H	H	CF_3	F	H	H	---	507.49	506

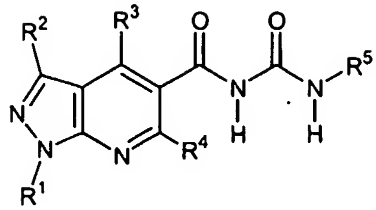
108	4-methyl-1,4-diazaperhydroepinyl	H	H	CF_3	F	H	H	HCl	543.95	ND
140	H	$Me_2NCH_2CH_2N(Me)$	H	O-iPr	H	H	H	HCl		
141	H	H	H	Cl	4-morpholinylcarbonyl	H	H	---		
142	H	H	H	Cl	4-methylpiperazinylcarbonyl	H	H	---		



V

Table 3

Cmpd	R	MW	MS(M+H) *(m/z)*	MS(M+H) *(m/z)*
134	4-methylpiperazine	480.42	481	479
135	4-methylpiperazine hydrochloride	516.88	481	479
136	dimethylamine	425.34	426	424
137	[2-(dimethylamino)ethyl] methylamine	482.43	483	481
138	[2-(dimethylamino)ethyl] methylamine hydrochloride	518.89	481	481
139	morpholine	467.37	468	466



VI

Table 4

Cmpd	R^1	R^2	R^3	R^4	R^5	MW	MS (m/z) (M-H)	MS (m/z) (M+H)
109	Me	Me	H	OH	4-fluoro-3-(trifluoromethyl)phenyl	411.32	410	412
110	Me	Me	H	1-methylethoxy	4-fluoro-3-(trifluoromethyl)phenyl	453.40	452	454
111	Me	Me	H	phenylmethoxy	4-fluoro-3-(trifluoromethyl)phenyl	501.44	500	502
112	Me	Me	H	methoxy	4-fluoro-3-(trifluoromethyl)phenyl	425.35	424	426
113	Me	Me	H	morpholine	4-fluoro-3-(trifluoromethyl)phenyl	480.43	479	481
114	Me	Me	H	dimethyl amine	4-fluoro-3-(trifluoromethyl)phenyl	438.39	437	439
115	Me	Me	H	4-methylpiperazine hydro chloride	4-fluoro-3-(trifluoromethyl)phenyl	529.93	492	494
116	Me	Me	H	[2-(dimethyl amino)ethyl] methylamine hydro chloride	4-fluoro-3-(trifluoromethyl)phenyl	531.94	494	496
117	Me	Me	H	2-(dimethyl amino) ethoxy hydro chloride	4-fluoro-3-(trifluoromethyl)phenyl	518.90	481	483
118	Me	Me	H	2-(dimethyl amino)iso propoxy hydro chloride	4-fluoro-3-(trifluoromethyl)phenyl	532.93	495	497
119	Me	Me	H	3-(dimethyl amino)pro poxy hydro chloride	4-fluoro-3-(trifluoromethyl)phenyl	532.93	495	497

Cmpd	R^1	R^2	R^3	R^4	R^5	MW	MS (m/z) (M-H)	MS (m/z) (M+H)
120	Me	Me	H	2-(diethyl amino) ethoxy hydro chloride	4-fluoro-3-(trifluo romethyl)phenyl	546.96	509	511
121	Me	Me	H	2-pyrrolidinyl ethoxy	4-fluoro-3-(trifluo romethyl)phenyl	544.94	507	509
122	Me	Me	H	2-piperidyl ethoxy	4-fluoro-3-(trifluo romethyl)phenyl	558.97	521	523
123	Me	Ph	H	H	4-fluoro-3-(trifluo romethyl)phenyl	457.39	456	458
124	Me	H	H	H	4-fluoro-3-(trifluo romethyl)phenyl	381.29	380	382
125	Ph	Me	H	H	4-fluoro-3-(trifluo romethyl)phenyl	457.39	456	458
126	Ph	Ph	4-methyl piper azine	H	4-fluoro-3-(trifluo romethyl)phenyl	617.61	616	618
127	Ph	Ph	4-methyl piper azine hydroc hloride	H	4-fluoro-3-(trifluo romethyl)phenyl	654.07	616	618
127	Me	Ph	4-methyl piper azine	H	4-fluoro-3-(trifluo romethyl)phenyl	555.54	554	556
129	Me	Ph	4-methyl piper azine hydroc hloride	H	4-fluoro-3-(trifluo romethyl)phenyl	592.00	554	556
130	Me	Me	H	Me	4-fluoro-3-(trifluo romethyl)phenyl	409.35	408	410
131	Me	Me	ethyl pipe ridine-4-carb oxylate	H	4-fluoro-3-(trifluo romethyl)phenyl	522.61	521	523
132	Me	Me	tert-butyl 2-amino acetate	H	4-fluoro-3-(trifluo romethyl)phenyl	496.57	495	497
133	Me	Me	tert-butyl 2-(methyl amino) acetate	H	4-fluoro-3-(trifluo romethyl)phenyl	510.60	509	511

The names of the compounds shown in Tables 1 to 4 are given in Tables 5 and 6. These names were generated with the Chemistry 4-D Draw™ software from ChemInnovation Software, Inc. (San Diego, CA).

Table 5

Cmpd	Name
1	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-fluorophenyl)amino]carbonyl}carboxamide
2	N-{[(3,4-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
3	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-chlorophenyl)amino]carbonyl}carboxamide
4	*N*-{[(2,4-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
5	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-chlorophenyl)amino]carbonyl}carboxamide
6	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-iodophenyl)amino]carbonyl}carboxamide
7	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-cyanophenyl)amino]carbonyl}carboxamide
8	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-bromophenyl)amino]carbonyl}carboxamide
9	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-chloro-4-hydroxyphenyl)amino]carbonyl}carboxamide
10	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
11	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
12	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[3-fluoro-4-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
13	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-nitro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
14	*N*-{[(2,3-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
15	*N*-{[(2,6-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
16	*N*-{[(2,5-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
17	*N*-{[(3,5-Dichlorophenyl)amino]carbonyl}(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
18	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[2-chloro-5-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
19	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-chloro-2-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide

Cmpd	Name
20	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[2-chloro-4-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
21	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
22	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[2,5-bis(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
23	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[3,4-bis(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
24	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[3-iodophenyl)amino]carbonyl}carboxamide
25	2-[4-({[(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)-2-chlorophenoxy]acetic acid
26	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
27	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-hydroxy-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
28	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[5-hydroxy-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
29	3-({[(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)carbonylamino)carbonyl}amino)-5-(trifluoromethyl)benzoic acid
30	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carboxamide
31	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-phenoxyphenyl)amino]carbonyl}carboxamide
32	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-phenylphenyl)amino]carbonyl}carboxamide
33	4-({[(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)-2-(1-methylethoxy)benzoic acid
34	Ethyl 2-[4-({[(1,3-dimethypyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)-2-(trifluoromethyl)phenoxy]acetate
35	2-[4-({[(1,3-Dimethypyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)-2-(trifluoromethyl)phenoxy]acetic acid
36	(4-Chloro-1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(3-chlorophenyl)amino]carbonyl}carboxamide
37	*N*-{[(3,4-Dichlorophenyl)amino]carbonyl}(4-chloro-1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
38	(4-Chloro-1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-({[4-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
39	(4-Chloro-1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-*N*-{[(4-chlorophenyl)amino]carbonyl}carboxamide
40	Sodium 2-[4-({[(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)-2-chlorophenoxy]acetate

Cmpd	Name
41	4-({[(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)carbonylamino]carbonyl}amino)benzoic acid
42	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide

Table 6

Cmpd	Name
43	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)(4-hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
44	[4-(Dimethylamino)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
45	(4-{[2-(Dimethylamino)ethyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
46	(4-{[2-(Dimethylamino)ethyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
47	(4-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
48	(4-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
49	(4-{[3-(Dimethylamino)propyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
50	(4-{[3-(Dimethylamino)propyl]amino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
51	{4-[bis(2-Hydroxyethyl)amino]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
52	{1,3-dimethyl-4-[(2-morpholin-4-ylethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
53	{1,3-Dimethyl-4-[methyl(1-methylpyrrolidin-3-yl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
54	{1,3-Dimethyl-4-[methyl(1-methylpyrrolidin-3-yl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
55	{4-[(4-Aminocyclohexyl)amino]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
56	{4-[(4-Aminocyclohexyl)amino]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride

57	{1,3-Dimethyl-4-[(perhydropyrrolizin-7a-ylmethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
58	{1,3-Dimethyl-4-[(perhydropyrrolizin-7a-ylmethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
59	{1,3-Dimethyl-4-[(2-perhydropyrrolizin-7a-ylethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
60	{1,3-Dimethyl-4-[(2-perhydropyrrolizin-7a-ylethyl)amino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
61	{1,3-Dimethyl-4-[benzylamino]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
62	{4-[3-(Dimethylamino)pyrrolidinyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
63	{4-[3-(Dimethylamino)pyrrolidinyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide, hydrochloride
64	(1,3-Dimethyl-4-piperidylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
65	(1,3-Dimethyl-4-morpholin-4-ylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
66	(1,3-Dimethyl-4-piperazinylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
67	(1,3-Dimethyl-4-piperazinylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
68	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-chlorophenyl)amino]carbonyl}carboxamide hydrochloride
69	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-bromophenyl)amino]carbonyl}carboxamide hydrochloride
70	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(4-chlorophenyl)amino]carbonyl}carboxamide
71	N-{[(3,4-Dichlorophenyl)amino]carbonyl}[1,3-dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]carboxamide
72	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
73	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
74	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-(methylethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
75	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carboxamide hydrochloride
76	4-[({[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]carbonylamino}carbonyl)amino]-2-(1-methylethoxy)benzoic acid
77	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-

	(trifluoromethoxy)phenyl]amino}carbonyl)carboxamide, hydrochloride
78	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-(1,3-thiazol-2-yl)phenyl)amino]carbonyl}carboxamide
79	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-(1,3-thiazol-2-yl)phenyl)amino]carbonyl}carboxamide hydrochloride
80	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-phenylphenyl)amino]carbonyl}carboxamide
81	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-phenylphenyl)amino]carbonyl}carboxamide hydrochloride
82	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-{[(3-phenoxyphenyl)amino]carbonyl}carboxamide
83	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-methyl-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
84	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
85	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
86	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-fluoro-4-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
87	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-hydroxy-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
88	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-hydroxy-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
89	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-hydroxy-5-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
90	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-hydroxy-5-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
91	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3,5-bis(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
92	Methylethyl 5-[({[1,3-dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]carbonylamino}carbonyl)amino]-2-chlorobenzoate hydrochloride
93	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-(phenylcarbonyl)phenyl]amino}carbonyl)carboxamide hydrochloride
94	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[3-chloro-4-(morpholin-4-ylcarbonyl)phenyl]amino}carbonyl)carboxamide
95	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-chloro-3-(morpholin-4-ylcarbonyl)phenyl]amino}carbonyl)carboxamide hydrochloride
96	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-[({4-chloro-3-[(4-methylpiperazinyl)carbonyl]phenyl}amino)carbonyl]carboxamide

97	[1,3-Dimethyl-4-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-[({3-chloro-4-[(4-methylpiperazinyl)carbonyl]phenyl}amino)carbonyl]carboxamide
98	[4-(4,4-Dimethylpiperazinyl)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide, iodide
99	[4-(4-Ethylpiperazinyl)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
100	[4-(4-Ethylpiperazinyl)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
101	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl){4-[4-(2-hydroxyethyl)piperazinyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}carboxamide
102	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl){4-[4-(2-hydroxyethyl)piperazinyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}carboxamide hydrochloride
103	[1,3-Dimethyl-4-(4-phenylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
104	{1,3-Dimethyl-4-[4-benzylpiperazinyl]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
105	{1,3-Dimethyl-4-[4-benzylpiperazinyl]pyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
106	4-Amino-1-{5-[N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carbamoyl]-1,3-dimethylpyrazolo[5,4-b]pyridin-4-yl}pyridinium chloride
107	[1,3-Dimethyl-4-(4-methyl(1,4-diazaperhydroepinyl))pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
108	[1,3-Dimethyl-4-(4-methyl(1,4-diazaperhydroepinyl))pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
109	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(6-hydroxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
110	[1,3-Dimethyl-6-(1-methylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
111	[1,3-Dimethyl-6-(phenylmethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
112	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(6-methoxy-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
113	(1,3-Dimethyl-6-morpholin-4-ylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
114	[6-(Dimethylamino)-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
115	[1,3-Dimethyl-6-(4-methylpiperazinyl)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide

	hydrochloride
116	(6-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
117	{6-[2-(Dimethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
118	{6-[2-(Dimethylamino)-isopropoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
119	{6-[3-(Dimethylamino)propoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
120	{6-[2-(Diethylamino)ethoxy]-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl}-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
121	[1,3-Dimethyl-6-(2-pyrrolidinylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
122	[1,3-Dimethyl-6-(2-piperidylethoxy)pyrazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
123	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(1-methyl-3-phenylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
124	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(1-methylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
125	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(3-methyl-1-phenylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
126	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[4-(4-methylpiperazinyl)-1,3-diphenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide
127	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[4-(4-methylpiperazinyl)-1,3-diphenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride
128	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[1-methyl-4-(4-methylpiperazinyl)-3-phenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide
129	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[1-methyl-4-(4-methylpiperazinyl)-3-phenylpyrazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride
130	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(1,3,6-trimethylpyrazolo[5,4-b]pyridin-5-yl)carboxamide
131	Ethyl 1-{1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carbamoyl]-

	pyrazolo[5,4-b]pyridin-4-yl}piperidine-4-carboxylate
132	tert-Butyl 2-({1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)-carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}amino)acetate carboxamide
133	tert-Butyl 2-({1,3-dimethyl-5-[N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)-carbamoyl]pyrazolo[5,4-b]pyridin-4-yl}methylamino)acetate
134	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[3-methyl-4-(4-methylpiperazinyl)isoxazolo[5,4-b]pyridin-5-yl]carboxamide
135	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-[3-methyl-4-(4-methylpiperazinyl)isoxazolo[5,4-b]pyridin-5-yl]carboxamide hydrochloride
136	[4-(Dimethylamino)-3-methylisoxazolo[5,4-b]pyridin-5-yl]-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
137	(4-{[2-(Dimethylamino)ethyl]methylamino}-3-methylisoxazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide
138	(4-{[2-(Dimethylamino)ethyl]methylamino}-3-methylisoxazolo[5,4-b]pyridin-5-yl)-N-({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)carboxamide hydrochloride
139	N-({[4-Fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)-(3-methyl-4-morpholin-4-ylisoxazolo[5,4-b]pyridin-5-yl)carboxamide
140	(6-{[2-(Dimethylamino)ethyl]methylamino}-1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[3-(1-methylethoxy)phenyl]amino}carbonyl)carboxamide
141	(1,3-Dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-({[3-chloro-4-(morpholin-4-ylcarbonyl)phenyl]amino}carbonyl)carboxamide
142	(1,3-dimethylpyrazolo[5,4-b]pyridin-5-yl)-N-[({3-chloro-4-[(4-methylpiperazinyl)carbonyl]phenyl}amino)carbonyl]carboxamide

Example 16: Inhibition of MCP-1-Induced Chemotaxis

A 96-well microchemotaxis chamber with a 5 μm-pore size, PVP-coated polycarbonate filter membrane (Neuro Probe Inc., Cabin John, MD) was used for testing. Compounds were prepared as 10 mM stock solution in DMSO. THP-1 cells ($2x10^6$ cells/mL) were labeled with 5 μM Calcein AM containing 0.1% F127 (Molecular Probe, Eugene, OR) at 37 °C for 30 min, and then pretreated with compound at room temperature for an additional 30 min. The lower chamber was loaded with medium containing 12.5 nM hMCP-1. The filter membrane was placed over the lower chamber, followed by a silicon gasket and the upper chamber. The pretreated THP-1 cells ($4x10^5$ cells/50μL of RPMI1640 medium

per well) were added to the upper chamber and incubated in 5% CO_2 at 37 °C for 2 h. The migrated cells were determined with a fluorescent plate reader (LJL BioSystems, Sunnyvale, CA). Table 7 shows the IC_{50} (concentration of compound that inhibited migration of 50% of the cells relative to control) for several compounds of the present invention.

Table 7: Effect of Selected Compounds on MCP-1 Induced Chemotaxis

Compound	IC_{50} (μM)
2	0.8
8	8.1
10	2.0
11	12.5
16	10.1
37	12.7
39	3.0

Example 17: Thioglycollate-Induced Inflammation Model

3% Brewer's thioglycollate broth (Difco, Detroit, MI) was injected into the peritoneal cavity of ICR male mice, followed by subcutaneous administration of the test compound. The same dose of test compound was again administered immediately after the broth injection and 3 h later. After 72 h, the number of total elicited cells and MOMA2- positive cells in the peritoneal cavity was analyzed using an EPICS XL Beckman Coulter. The results are shown in Table 8.

Table 8[a]: Effect of Compound 11 on a Thioglycollate-Induced Inflammation Model

Compound	Dose (mg/kg)	Total Cells ($x10^6$)	MOMA2-positive Cells ($x10^6$)
No treatment	-	2.1 ± 0.3**	1.2 ± 0.2**
Control	-	24.4 ± 1.1	18.5 ± 0.9

11	5	19.7 ± 1.6	14.3 ± 1.2*
Anti-MCP-1 Ab	1	12.3 ± 1.8**	8.8 ± 1.2**

[a]Anti-MCP-1 Ab was intraperitoneally injected. Significant difference from control group:

*P<0.05, **P<0.01 (ANOVA).

Example 18: Thioglycollate-Induced Inflammation Model

3% Brewer's thioglycollate broth (Difco, Detroit, MI) was injected into the peritoneal cavity of ICR male mice, followed by subcutaneous administration of the test compound. The same dose of test compound was again administered immediately after the broth injection and 3h later. After 72 h, the number of total elicited cells and MOMA2- positive cells in the peritoneal cavity was analyzed using an EPICS XL Beckman Coulter. The results are shown in Table 9.

Table 9.[a] Effect of Compounds on a Thioglycollate-Induced Inflammation Model

Compound	Dose (mg/kg)	Total Cells ($x10^6$)	MOMA2-positive Cells ($x10^6$)
No treatment	-	1.9±0.2**	0.9±0.1**
Control	-	9.6±0.7	7.8±0.6
142	10	7.5±1.2	5.5±0.4
140	10	7.3±1.1	5.2±0.6*
116	10	4.2±1.1*	3.0±0.8**
97	2	6.4±0.6	4.1±0.3**

[a] Significant difference from control group: *P<0.05, **P<0.01 (Least Significant Difference Method).

Example 19: Anti-Thy-1 Antibody-Induced Nephritis Model

The efficacy of the compounds of the present invention was also evaluated in an animal model of nephritis. This model very closely simulates the conditions found in human mesangial proliferative glomerulonephritis.

Anti-Thy-1 nephritis was induced by intravenous injection of anti-Thy-1-antibody to male Wistar rats. The test compound was subcutaneously administered 2 h before, immediately after, and 5 h after the anti-Thy-1 antibody treatment, and then twice a day for the following 2 days. Anti-MCP-1 antibody was intraperitoneally injected once a day for 3 days. Seven days after the anti-Thy-1 antibody treatment, the rats were sacrificed. The kidneys were perfused with 10% formaldehyde in PBS, surgically removed, and immersed in 10% formaldehyde. The kidneys were then embedded in paraffin for glomerular histopathology or in OCT compound (Miles Inc., Elkhart, IN) in liquid nitrogen after immersion in 30% sucrose overnight. Immunohistochemical staining was performed with a mouse anti-rat ED-1 monoclonal antibody. Briefly, 5 µm renal sections were prepared and endogenous peroxidase blocked with 0.3% hydrogen peroxide. The sections were then blocked with Protein Block (DAKO, Japan) and stained with anti-ED-1 antibody for 45 min. The ED-1 antigen was visualized by peroxidase-labeled anti-mouse IgG and diaminobenzidine. The amount of urinary protein was determined with the DC protein assay kit (Bio-Rad, Hercules, CA). The effect of a representative test compound on the level of urinary protein excretion and the infiltration of ED-1 positive cells into the glomeruli is shown in Table 10.

Table 10[a]: Effect of Compound <u>11</u> on Anti-Thy-1 Antibody Induced Nephritis

Compound	**Dose (mg/kg)**	**Urinary Protein (mg/day)**	**ED-1 positive cells/glomeruli (mean±SE)**
No treatment	-	20.5 ± 3.4**	0.2 ± 0.1
Control	-	277.8 ± 24.2	7.8 ± 1.1
<u>11</u>	0.1	182.2 ± 28.0	5.3 ± 0.7
<u>11</u>	2	117.4 ± 26.3	2.3 ± 0.6**

Anti-MCP-1 Ab	1	137.2 ± 57.4**	6.2 ± 0.9

[a]Significant difference from control group: **P<0.01 (ANOVA).

Example 20: Apolipoprotein E-Deficient Mouse Model

Apolipoprotein E (apoE) is a component of several plasma lipoproteins, including chylomicrons, VLDL, and HDL. Receptor-mediated catabolism of these lipoprotein particles is mediated through the interaction of apoE with the LDL receptor (LDLR) or with LDLR-related protein (LRP). ApoE-deficient mice exhibit hypercholesterolemia and develop complex atheromatous lesions similar to those seen in humans. The efficacy of the compounds of the present invention was also evaluated using this animal model.

Male, 4 week-old apoE-deficient mice were fed on high-fat diet (15% fat, 1.25% cholesterol). The test compound was administered as food admixture for 8 weeks. At 12 week-old, the mice were fasted for 4 hours and then sacrificed under ether anesthesia. Blood was collected in the presence of heparin, and the hearts were perfused *in situ* with PBS (pH 7.4), followed by 4% paraformaldehyde for 5 min.

To determine cross-sectional lesion areas, the hearts were embedded in OCT compound and sectioned at 10 μm using cryostat. The sections were stained with oil red O. Each section of the aortic valve was evaluated for oil red O staining by capturing images directly from a RGB camera attached to a light microscope; image analysis was performed with the IPAP-WIN software (Sumika Tekuno, Japan). Five sections were examined for each animal, and the sum of the lesion areas was calculated and expressed as the percent of the total cross-sectional wall area. Total cholesterol was determined with a Determiner assay kit (Kyowa medex, Japan).

The effect of a representative test compound in this animal model of atherosclerosis is shown in Table 11.

Table 11[a]: Effect of Compound 11 on the ApoE-Deficient Mouse Model of Atherosclerosis

Compound	Dose (mg/kg)	% Atherosclerotic Lesion (mean±SD)
Control	-	25.08 ± 6.93
11	10	18.72 ± 5.27*

[a]Significant difference from control group: *P<0.05 (t-test).

Compound 11 reduced the percent of atherosclerotic lesion area and this reduction was statistically significant. There were no significant differences in plasma total cholesterol level and body weight between the control and the test compound-treated groups (data not shown).

Example 21: Inhibition of MCP-1-Induced Chemotaxis

A 48-well microchemotaxis chamber with a 5 μm-pore size, PVP-coated polycarbonate filter membrane (Neuro Probe Inc., Cabin John, MD) was used for testing. Compounds were prepared as 10 mM stock solution in DMSO. THP-1 cells were washed with RPMI 1640 medium supplemented with 0.5% BSA and 25 mM HEPES, pH 7.4, and suspended at a density of $4x10^6$ cells/mL in the same medium. A 150 μL aliquot of this suspension was treated with an equal volume of test compound solution and the mixture incubated at 37 °C for 15 min. The lower chamber was loaded with 26 μL of a 2.5 nM solution of hMCP-1 (PeproTech) in medium. The filter membrane was placed over the lower chamber, followed by a silicon rubber gasket and the upper chamber. A 50 μL aliquot of the THP-1 cell suspension containing the test compound was added to the upper chamber and the assembly incubated in a 5% CO_2 atmosphere at 37 °C for 2 hr. The chamber was then disassembled and the cells remaining on the upper surface of the filter were scrapped off with a rubber scrapper. The filter was fixed with methanol, stained with Diff-Quik solution, and mounted on a slide glass. The cells that had migrated across the filter onto the lower surface were then counted by microscopic observation. Table 12 shows the IC_{50} (concentration of compound that inhibited migration of 50% of the cells relative to control) for several compounds of the present invention.

Table 12: Effect of Selected Compounds on MCP-1-Induced Chemotaxis

Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)
43	7.7	**64**	2	**77**	0.7	**92**	2.1
44	8.2	**65**	10	**78**	0.9	**94**	1.2
46	2	**67**	1.8	**79**	3	**95**	1.9
48	2	**68**	4	**80**	4	**97**	1.1
50	10	**69**	4	**81**	4	**100**	0.38
51	1.6	**70**	4	**83**	4	**102**	2
54	0.4	**71**	4	**85**	0.09	**103**	2
56	0.4	**72**	3.6	**87**	4	**105**	2
58	10	**73**	1.7	**88**	4	**106**	0.4
60	1.2	**74**	4	**89**	4	**108**	2
61	20	**75**	0.7	**90**	4		
63	1.2	**76**	4	**91**	3		